

**OBSERVATIONS ON PUVA TREATMENT
OF PSORIASIS
AND ON 5-S-CYSTEINYLDOPA
AFTER EXPOSURE TO
UV LIGHT**

**BY
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LUND 1983**

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To my Family



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by

Rahms i Lund

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This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. Tegner, E.: Oral 8-methoxypsoralen photochemotherapy of psoriasis. A follow-up study of 302 patients. In this supplement.
- II. Tegner, E.: Severe skin pain after PUVA treatment. *Acta Dermatovener (Stockholm)* 59:467, 1979.
- III. Tegner, E.: Seborrhoeic dermatitis of the face induced by PUVA treatment. *Acta Dermatovener (Stockholm)* 63:00, 1983.
- IV. Agrup, G., Hansson, C., Rorsman, H., Rosengren, A.-M., Rosengren, E. & Tegner, E.: 5-S-Cysteinyldopa excretion after treatment with 8-methoxypsoralen and UVA light. *J Invest Dermatol* 70:25, 1978.
- V. Hansson, C., Rorsman, H., Rosengren, E. & Tegner, E.: 5-S-cysteinyldopa and dopa in serum during treatment with 8-methoxypsoralen and UVA light. *Acta Dermatovener (Stockholm)* 61:251, 1981.
- VI. Tegner, E., Rorsman, H. & Rosengren, E.: 5-S-cysteinyldopa and pigment response to UVA light. *Acta Dermatovener (Stockholm)* 63:21, 1983.
- VII. Tegner, E., Agrup, G. & Rosengren, E.: The effect of UVB light on serum concentrations of 5-S-cysteinyldopa. *Acta Dermatovener (Stockholm)* 63:149, 1983.

INTRODUCTION

The conventional axiom that the sun cures human illness comes to us from ancient times and persists to this day. Most people believe that sunlight is highly beneficial to health, and they expose themselves to it whenever they can – in the mountains, on the beach, and under sun lamps.

Psoriasis is a skin disease found throughout the world. In a northern European population the prevalence of psoriasis is about 2% (32, 49). It has been known for centuries that psoriasis often improves after repeated sun exposure during the summer months.

In about 1890 artificial ultraviolet (UV) light from a carbon arc was first used in the treatment of skin disorders by Finsen. The popularity of UV light therapy increased with the invention of the mercury vapour lamp in about 1905. Goeckerman was an early advocate of this light source. He acknowledged the efficacy of ultraviolet radiation alone in the treatment of psoriasis, but went further and suggested that the prior application of an ointment containing crude coal tar followed by exposure to radiation from the hot quartz mercury vapour lamp was more successful in treating psoriasis than either agent alone (22). In 1953 Ingram described an efficient method for treating psoriasis where he combined a coal-tar bath, UV light, and a stiff dithranol paste (38).

There have been conflicting reports about the value of UV light in psoriasis when used alone. Young found little or no antipsoriatic effect, but the period of observation was short (91). Others have found UV light to be useful in the treatment of psoriasis (20, 55). The radiation in the UVB region (280–315 nm) is believed to be the most effective (20). At present there is a trend back to the old use of UVB phototherapy of psoriasis (1, 10, 44, 47, 58, 86), and, paradoxically, the introduction of psoralen-UVA photochemotherapy has also aroused interest in UVB treatment of psoriasis.

PUVA (psoralen and UVA) is a specific form of photochemotherapy consisting of oral administration of psoralen and subsequent exposure of the skin to long-wave UV light (UVA: 320–400 nm). Psoralens are naturally-occurring, tricyclic, furocoumarin-like compounds, some of which can be activated by UVA to elicit phototoxic reactions. 8-Methoxypsoralen (8-MOP) is a derivative of psoralen itself, and is the most commonly used in medicine. Previously, 8-MOP was used to induce repigmentation in vitiligo (45).

The rationale for the use of PUVA in the treatment of psoriasis is inhibition of the increased DNA synthesis within keratinocytes of the psoriatic lesions. This inhibition is accomplished by a specific interaction between psoralen and DNA molecules that involves absorption of radiant energy in the UVA range. Absorption of photons in the UVA spectrum transforms psoralen molecules into a photoexcited state. This results in photoconjugation of psoralen with the pyrimidines of DNA, leading to interstrand cross-linkages between a single psoralen molecule and opposite pyrimidine bases. Presumably, this process leads to inhibition of DNA synthesis, and thus of cell division, within the rapidly dividing cells of the psoriatic epidermis (60).

In 1974 the first full-scale PUVA trial for the treatment of psoriasis was reported by Parrish et al (61), who utilized a powerful, newly developed artificial source of UVA. Detailed studies in the USA and Europe have since shown PUVA to be a highly effective form of treatment (14, 18, 30, 33, 34, 50, 69, 70, 77, 79, 82, 85, 87, 89).

Few known efficient treatments for any disease are without drawbacks, and these must always be weighed against the benefits. Numbers of acute side effects of PUVA treatment have been reported, of which pruritus, nausea, and erythema are the commonest (33, 50, 70, 81, 85, 89).

The acute side effects can be managed, but doubt remains concerning the long-term side effects, particularly the increased risk of developing skin cancer reported in PUVA-treated patients (13, 36, 37, 80).

One of the side effects of PUVA treatment is powerful stimulation of pigmentation, – and this is usually much relished by the patient. An increase in the number of functionally active melanocytes has been reported (63, 64, 93), but has not been confirmed by others (75). Melanosomes increase in number (63, 64, 92, 93) and size (67). Increased tyrosinase activity in the melanocytes has been observed after PUVA treatment (64).

Among the metabolites of the melanocytes dopa and 5-S-cysteinyl-dopa have a key role (72). Both are formed by the action of tyrosinase, dopa from tyrosine and 5-S-cysteinyl-dopa from dopa by oxidation to dopaquinone followed by nucleophilic addition of cysteine (72). In recent years cysteinyl-dopas have become highly interesting as biochemical recorders of malignant melanoma (2, 3, 4), and among them 5-S-cysteinyl-dopa has attracted the greatest attention because it is quantitatively the most important (72). Several methods have been developed for its

analysis: fluorimetry initially proved the most useful for routine estimation of 5-S-cysteinyldopa in urine (73). Now liquid chromatography with electrochemical detection seems more valuable for investigative studies and for determination of 5-S-cysteinyldopa in urine, tissues, serum, and plasma (26, 43).

The urinary excretion of 5-S-cysteinyldopa is increased in most patients with disseminated malignant melanoma (4). However, this substance is also excreted in the urine by normal subjects (5). In a study on inhabitants of Lund, Sweden, it was found that the quantity excreted varied with the season of the year, being greatest in summer, intermediate in spring and autumn, and least in winter (71), which suggests that the UV-stimulated melanocytes produce increased amounts of cysteinyldopa.

In December 1975 PUVA therapy was started at this department in accordance with the principles of the European Cooperative Clinical Trial (Wolff et al, 89), and the department contributed the first 117 PUVA-treated patients in a co-ordinated European multicentre study (33). The powerful stimulation of pigmentation achieved by PUVA inspired a series of investigations concerning the effect on 5-S-cysteinyldopa of various forms of treatment using artificial UV light with and without psoralens. During the course of treating patients and in our pigment studies we have made certain clinical observations, which are reported.

THE PRESENT STUDY

The following subjects are discussed.

- The clinical material consisting of 302 patients treated with PUVA – the effects and side effects.
- The occurrence of 2 previously unreported side effects of PUVA treatment – severe skin pain and seborrhoeic dermatitis of the face.
- The urinary excretion of 5-S-cysteinyldopa and the serum concentrations of 5-S-cysteinyldopa and dopa after PUVA treatment.
- The serum concentrations of 5-S-cysteinyldopa after exposure to UVA and UVB light.
- The preventive effect of external pressure on erythema and pigmentation induced by UVA light.

MATERIAL AND METHODS

A. CLINICAL STUDIES ON PUVA – EFFECTS AND SIDE EFFECTS

Oral 8-methoxypsoralen photochemotherapy of psoriasis. A follow-up study of 302 patients (I)

Severe skin pain after PUVA treatment (II)

Seborrhoeic dermatitis of the face induced by PUVA treatment (III)

Over a period of 5 1/2 years (December 1975 to July 1, 1981) 181 men and 121 women with widespread psoriasis, mostly of chronic plaque type, were treated with PUVA. The mean duration of illness before the first PUVA treatment was 26.5 years. Details are given in a special section of this supplement (page 48).

Before starting treatment the sensitivity to sun and the ability to tan were estimated on an established sensitivity scale (50). All patients were white, and most had skin types II and III.

To establish the initial UVA dose all patients were phototested in accordance with the principles set out by Wolff et al (90). They were given 20–60 mg of 8-methoxypsoralen according to body-weight (0.6 mg/kg), followed by irradiation after 2 hours. This procedure was carried out 4 times weekly.

The light source was a high-intensity UVA system (PUVA 4000, Sylvania) with an emission spectrum between 320 and 390 nm, a peak emission of 365 nm, and an energy of 5.6–7.5 mW/cm² at 15 cm. As a rule the initial UVA dose was well below the minimum phototoxic dose (MPD). In most cases the dose was increased once per week, and then by 0.5 J/cm² at each session. Treatment was classified as initial course, maintenance course, and repeated courses of PUVA treatment.

During the initial course patients were treated 4 times weekly until the lesions cleared. The highest initial UVA dose was 4 J/cm², even when the MPD was high (5–9 J/cm²). After the initial course treatment was stopped in all but 34 patients.

34 patients, i.e. only about 1/10 of the series, were given maintenance treatment. Most had very severe psoriasis that had taken long to clear. The frequency of sessions ranged from once weekly to once every second week. The last effective UVA dose in the initial course was used for maintenance treatment. If new lesions appeared the UVA dose was increased by 0.5 J/cm^2 at every second session.

After the initial course patients were followed for up to 5 1/2 years, clinical examination being made every 3 to 6 months. When relapse occurred one or more repeated courses of PUVA treatment were given in 152 cases, as a rule with 4 treatment sessions per week, but in 19 patients with 2 sessions per week.

Laboratory tests including erythrocyte sedimentation rate, haemoglobin concentration, red blood cell count, white blood cell count, thrombocyte count, blood glucose, liver function tests, serum creatinine, urine analysis, and antinuclear antibodies (ANA) were done before treatment, after 1 and 3 months, and every third month during maintenance treatment.

Before treatment ophthalmological examination was performed, with reexamination if a new course of treatment was instituted. The eyes were protected with small opaque goggles during irradiation. All patients were instructed to wear sunglasses conferring protection against UVA throughout the day of medication with psoralen (88).

Naevi and skin lesions were particularly noted. In 3 patients junction naevi were excised before PUVA treatment was started. In some others biopsy was done on non-pigmented lesions suspected of malignancy during or after the treatment.

Note was made of the occurrence of previously reported side effects of PUVA treatment, and with time also of two previously unreported side effects – severe skin pain and seborrhoeic dermatitis of the face.

B. LABORATORY STUDIES ON 5-S-CYSTEINYLDOPA AND DOPA

5-S-cysteinyldopa excretion after treatment with 8-methoxypsoralen and UVA light
(IV)

5-S-cysteinyldopa and dopa in serum during treatment with 8-methoxypsoralen and UVA light (V)

5-S-Cysteinyldopa and pigment response to UVA light (VI)

The effect of UVB light on serum concentrations of 5-S-cysteinyldopa (VII)

ANALYTICAL METHODS

1. Fluorimetric determination of 5-S-cysteinyldopa in urine

24-hour specimens of urine were collected in plastic bottles containing 50 ml of acetic acid and 1 gm of sodium metabisulphite. 20 ml of urine was adsorbed onto Al_2O_3 and eluted with 0.1 M HCl. The 5-S-cysteinyldopa in the eluate was determined fluorimetrically (73).

2. High-performance liquid chromatographic (HPLC) determination of 5-S-cysteinyldopa and dopa in serum

10 ml samples of venous blood were collected in glass tubes containing 10 mg sodium metabisulphite. The samples were centrifuged at 4500 rpm for 10 min within 1 h. Serum proteins were precipitated with 1/10 volume 4-M perchloric acid. The samples were centrifuged at 15 000 rpm. and filtered. 5-S-Cysteinyldopa and dopa were adsorbed onto Al_2O_3 at pH 8.6, eluted with perchloric acid, and then determined by HPLC and electrochemical detection (26).

SUBJECTS STUDIED, LIGHT-EXPOSURE, AND SAMPLING SCHEDULES

1. 5-S-cysteinyldopa in urine and serum after PUVA treatment

15 patients with severe generalized symmetrical psoriasis but otherwise healthy were studied. None was receiving any drug other than 8-methoxypsoralen. There had been no exposure to strong sunlight or other ultraviolet light during the 1 to 3 months preceding the investigation (71). The 8-methoxypsoralen administration, treatment schedule, and light source are described on page 9.

Urine was collected from 5 patients immediately before commencing PUVA treatment, after 2 sessions, after treatment for 1 week, and subsequently each week until the lesions had healed. Urine was not collected during the 24 h after intake of 8-methoxypsoralen, because such samples contain a fluorophore that could interfere with our 5-S-cysteinyldopa measurements.

Blood samples were collected before treatment and, in 4 patients, almost every day for the first 8 days of treatment, and in 6 patients after 1, 3, 7, 10, 14, 21, and 28 days' treatment.

3 patients with psoriasis localized to the palms and/or soles only were treated 3 times weekly, local irradiation being provided by a small PUVA unit (PUVA 180 combined with PUVA 200, Sylvania); the initial dose of UVA was 2.5 J/cm^2 and was increased by 0.5 J/cm^2 at every second session (56). These 3 patients were investigated during 30–40 days' treatment, blood samples being taken before treatment and then at intervals of 5–7 days.

2. 5-S-cysteinyl-dopa in serum after exposure to UVA light

10 healthy volunteers were studied. None was taking drugs, and there had been no exposure to strong sunlight or other ultraviolet radiation during the 2–3 months before the investigation.

The light source was a high-intensity UVA system (Philips TL 85 W/09 T) with an emission spectrum of 310–420 nm and a peak emission of 355 nm. About 0.4% of the radiant energy output is in the UVB region. The light source consisted of 10 tubes beneath a transparent plate of acrylic plastic for the individual to lie on. Using a Waldmann UVA-meter (H. Waldmann Werk für Lichttechnik, Germany) the intensity of the lamps in the UVA region primarily around the 360 nm band was estimated to 11 mW/cm^2 just above the plate. Skin was exposed, front and back, for 30 minutes on each side on each of 10 successive days.

Blood samples were collected 3 days before and just before the UVA irradiation series was started, and after 1, 3, 4, 7, 8, and 10 days' irradiation. In 4 persons a further blood sample was collected 18 days after starting irradiation, i.e. 9 days after completing the course of irradiation.

3. 5-S-cysteinyl-dopa in serum after treatment with UVB light

12 otherwise healthy patients with moderate psoriasis were included in the study. None was receiving any drugs. There had been no exposure to strong sunlight or other ultraviolet radiation during the 2–3 months preceding the investigation.

The light source was a UVB cabin (Waldmann Radiation Unit UV 1000) with an emission spectrum between 280 and 380 nm and a peak emission of 313 nm. The intensity of the lamp in the UVB region was measured with a Waldmann UV-Meter. At

a distance of 20 cm from the tubes the intensity was estimated to 2.2 mW/cm^2 . 4 treatments per week were given. The initial dose was 20–30 sec, depending on skin type, and as a rule the exposure time was increased by 20–30 sec at each session. The exposure times were chosen to give slight erythema throughout the treatment period.

Blood samples were collected before the UVB treatment series started, and after 1, 3, 7, 10, 14, and 21 treatments. In 7 patients a further blood sample was collected after 28 treatments.

4. Dopa in serum after PUVA treatment

6 patients with severe generalized symmetrical psoriasis but otherwise healthy were studied. None was receiving drugs other than 8-methoxypsoralen. There had been no exposure to strong sunlight or other ultraviolet light during the 1–3 months preceding the investigation. The 8-methoxypsoralen administration, treatment schedule, and light source are described on page 9.

Blood samples were collected before treatment and after 1, 3, 7, 10, 14, 21, and 28 days' treatment.

C. CLINICAL OBSERVATIONS ON THE EFFECT OF EXTERNAL PRESSURE ON ERYTHEMA AND PIGMENTATION INDUCED BY UVA LIGHT

5-S-cysteinyldopa and pigment response to UVA light (VI)

The immediate pigment darkening (IPD), the delayed tanning (DT), and the occurrence of erythematous reactions were studied in connection with each irradiation in 10 subjects receiving UVA in accordance with the principles outlined above (page 12). A shielded rectangular area on one buttock served as control for judging erythema and pigmentation on exposed areas.

RESULTS

A. CLINICAL STUDIES ON PUVA – EFFECTS AND SIDE EFFECTS

1. Efficacy of PUVA treatment (I)

Complete clearing or definite improvement was obtained in 96% of the 302 PUVA-treated patients. An average of 26 treatment sessions with a total cumulative UVA dose of 80 J/cm^2 were required for clearing, the duration of the initial PUVA course being 7 weeks. Without maintenance treatment patients stayed in remission for 6 months (average). Of the 34 patients given maintenance treatment 21 had shown complete clearing during the initial course. They all remained in remission throughout the 5-months' (average) maintenance course, during which they received 73 J/cm^2 (average). After discontinuation of the maintenance course of treatment the patients stayed in remission for 5 months (average). 50% of the 302 patients received one or more repeated courses of PUVA treatment. The number of sessions, the total UVA dose needed for clearing, and the remission time were the same for the first and second courses. Some patients were given an initial course with 4 sessions per week and a second course with 2 sessions per week. The total number of sessions was the same in each, but treatment took twice as long with 2 sessions per week (5 compared to 10 weeks); and with 2 sessions per week the total UVA dose was higher. The average remission time was the same after both modes of treatment.

2. Side effects of PUVA treatment (I, II, III)

The commonest acute side effects (starting during or within a couple of weeks after ending treatment) were pruritus (16%), nausea (6%), seborrhoeic dermatitis of the face (6%), and skin pain (5%). Details are given on page 63.

Of the long-term side effects the commonest was "localized" hyperpigmentation, which occurred in 2% of the patients; this is to be distinguished from the general diffuse hyperpigmentation achieved by PUVA treatment. In patients given a total cumulative UVA dose of about 1000 J/cm^2 or more, disseminated spots of hyperpigmentation – lentiginosis – appeared. Biopsy showed in the epidermis slight elongation of the rete ridges and focal basal melanin hyperpigmentation. The melanocytes were slightly distended and rather densely arranged. There were no naevus-cell nests. When PUVA treatment was discontinued the lentiginosis faded

very slowly. In a few patients the hyperpigmentation resembled naevus spilus, developing in earlier psoriatic lesions and disappearing in time. Hypopigmentation with the clinical appearance of pityriasis alba was seen in 5% of our patients after prolonged therapy. A 55-year-old man with skin type I developed squamous-cell carcinomas on the right leg. He was the only patient in the series who received a cumulative UVA dose of more than 1500 J/cm^2 (1750 J/cm^2). He had also sunbathed and used artificial UVB light for many years, however. He had never been given arsenic or X-radiation, but for a short time received methotrexate therapy. A 60-year-old woman with skin type II developed a basal-cell carcinoma on the dorsum, and another developed actinic keratosis of the face.

As a rule the laboratory tests were normal. 2 patients showed a pronounced rise in serum transaminases, which returned to normal when PUVA treatment was discontinued. Serum antinuclear antibodies (ANA) were studied before and during PUVA treatment: positive tests appeared to be largely transient and unstable, and most became negative. No ophthalmological changes attributable to the treatment were recorded. No changes in naevi motivating excision were noted.

A troublesome effect of PUVA treatment was extremely severe skin pain, usually starting about 1 week after finishing the PUVA course, coming in attacks lasting for several hours, and persisting for 1–3 months. The pain was described as a prickling, burning sensation confined to limited areas "deep under the skin". All patients with this pain complained also of itching before, together with, or after the development of the pain, but they could readily distinguish between the two sensations. The state was dramatic and rendered some patients bedridden. Two described it as "worse than renal colic". Up to July 1981, 15 psoriatic patients had suffered from it. 7 are described in detail (II). 5 patients with skin pain were given repeated courses of PUVA treatment when the psoriasis recurred: 3 received 4 sessions per week (as during the initial course of treatment), and all developed pain again; 2 were treated only twice weekly during the second course and had no relapse of pain (84). A patient in whom skin pain reappeared during the second 4-day/week course was treated twice weekly during a third course, and this time no pain occurred.

The total and maximum UVA doses were small in all cases. There was no obvious correlation between the occurrence of pain and the skin type and MPD of the patients.

The pain demanded treatment owing to its intensity, and several drugs were tried but with poor effect.

Neurological examination (performed in all 15 patients), motor and sensory neurography (2 patients), histopathological examination (3 patients), examination by direct immuno-fluorescence (2 patients), and electron microscopy (2 patients) yielded no clues. In one patient neurophysiological examination indicated a selective stimulation of nociceptive afferents in the skin. There were no signs of generalized peripheral neurotoxic influence.

A form of seborrhoeic dermatitis of the face was observed in 28 of 347 patients treated with PUVA for psoriasis. This appeared after discontinuation of PUVA, was not present at the start of PUVA treatment, and could be prevented by masking the face during irradiation. The lesions were red, scaling, often slightly itching, and located between the eyebrows, in the eyebrows, in the nasolabial folds, and very characteristically on the cheeks near the nose. Biopsy of skin was performed in 3 patients, and the findings confirmed the clinical diagnosis. There was often fine scaling of the scalp, sometimes in combination with common psoriasis.

A new PUVA series given for psoriasis of the trunk cleared up the facial lesions, which however recurred soon after discontinuation of treatment. Among the 28 patients with PUVA-induced facial dermatitis some recalled a burning sensation in the face during irradiation, and in a few others mild facial erythema occurred during treatment. In this group of patients localized erythema on other parts of the body was common during treatment. 5 of the 28 developed phototoxic blisters on the feet and legs, 1 showed bleeding under the fingernails, and 4 complained of severe skin pain.

Of the patients with facial dermatitis after PUVA, 1 had skin type I and all the others skin types II and III. The MPD varied between 0.5 and 9 J/cm². The total UVA dose given up to the time facial dermatitis was first noted varied between 24 J/cm² and 304 J/cm².

B. LABORATORY STUDIES ON 5-S-CYSTEINYLDOPA AND DOPA

1. 5-S-Cysteinyldopa in urine and serum after PUVA treatment (IV, V)

The urinary excretion of 5-S-cysteinyldopa and the concentration of 5-S-cysteinyldopa in serum before treatment was in every case within the normal range (5, 27, 28). After 3 days (2 PUVA treatments) 5-S-cysteinyldopa values were raised in most patients (Figs. 1, 2, and 3). At this time there was no increase in pigmentation, which was first noted after about 1 week's treatment. The maximum urinary excretion and serum concentration were recorded after 4-8 treatments, i.e. after 7-14 days. In the patients with the highest values (Figs. 1 and 3) widespread erythema was present at the same time. After 3 weeks' treatment the urinary excretion was lower than at the second week, but the subsequent findings varied from patient to patient. The high serum values sometimes noted after 3 weeks' treatment was accompanied by localized erythema in 2 patients (Fig. 3, C.N. and A.H.) or by marked hyperpigmentation on the knees and medial malleoli in 1 (F.S.).

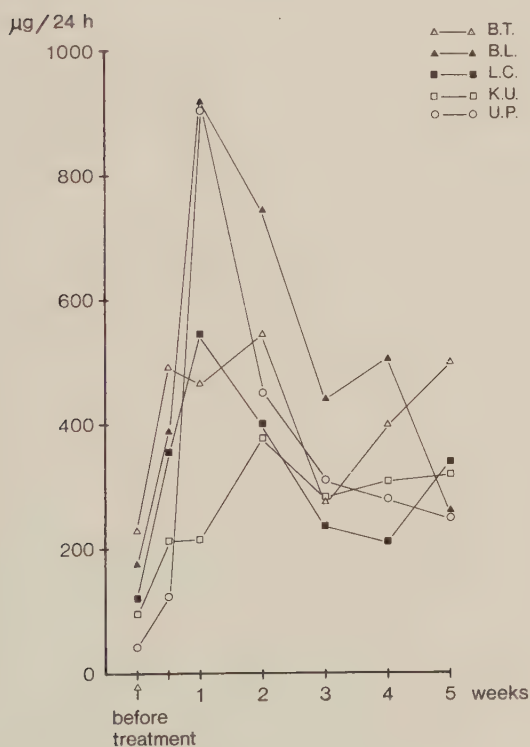


Fig. 1. Urinary excretion of 5-S-cysteinyldopa during 5 weeks of PUVA treatment.

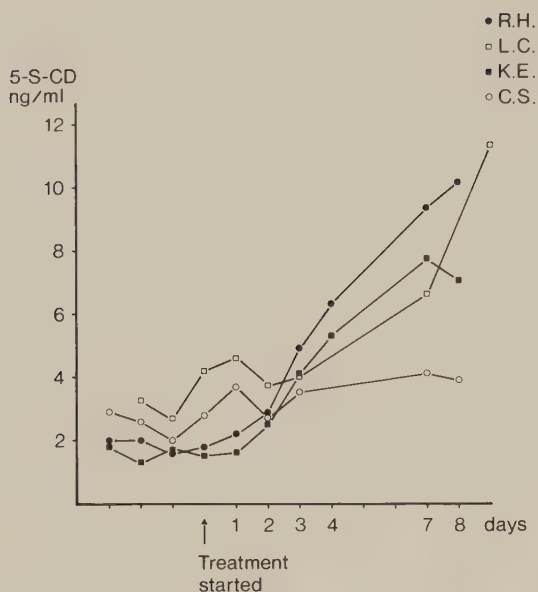


Fig. 2. Serum concentration of 5-S-cysteinyldopa during the first week of PUVA treatment.

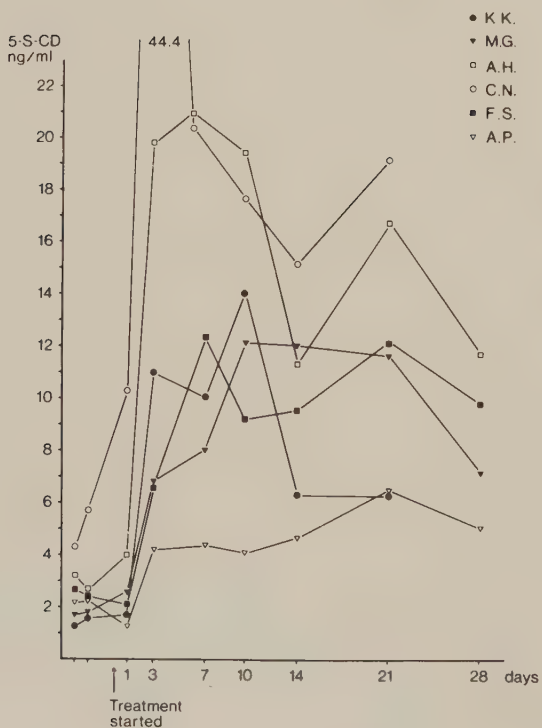


Fig. 3. Serum concentration of 5-S-cysteinyldopa during 4 weeks of PUVA treatment.

The psoriasis lesions cleared in all but 1 patient after 3–10 weeks' treatment. All but 2 developed pronounced tanning. Pigmentation was most prominent in the previously affected skin areas. 2 patients (C.S. and A.P.) developed only a slight tan and the increase in serum concentration of 5-S-cysteinyl dopa was small (Table I). In 1 patient (C.S.) the psoriasis failed to clear during PUVA treatment, which was discontinued after 30 sessions. After 18 sessions the serum concentration of 5-S-cysteinyl dopa was the same as before treatment. As the psoriasis did not respond to treatment the plasma concentration of 8-methoxypsoralen was measured 2 h after taking the drug (48). The 8-MOP plasma concentration was 0.60 $\mu\text{mol/l}$, which is within the normal range. In 1 patient (A.P.) the psoriasis cleared, but recurred only 2 weeks after stopping treatment.

Table I. Clinical and biochemical data in patients treated with PUVA

Pa- tient	Age	Sex	Hair colour	Eye colour	Skin type*	MPD (J/cm ²)**	Initial PUVA dose (J/cm ²)	5-S-Cysteinyl dopa (ng/ml)	
								Initial value	Max. value
R.H.	31	M	Blond	Green	III	1.5	1	2.0	10
F.S.	68	M	Brown	Brown	II	2	1.5	2.4	12
K.E.	28	F	Blond	Blue	II	2	2	1.3	7.6
M.G.	50	F	Blond	Green	II	3	2.5	1.7	12
A.H.	22	M	Blond	Blue	II	3	2.5	2.7	21
C.N.	40	M	Blond	Grey	III	3	2.5	4.3	44
A.P.	48	M	Blond	Blue	II	4	2.5	2.2	6.5
L.C.	53	M	Brown	Green	IV	3	3	1.3	6.2
C.S.	20	F	Blond	Blue	III	7	3	2.9	4.1
K.K.	30	M	Blond	Blue	III	5	3.5	1.3	14

* The following criteria were used: Skin type I = always burn, never tan; II = always burn, then light tan; III = sometimes burn, always tan; IV = never burn, always tan.

** MPD = the patient's minimum phototoxicity dose.

The serum concentration of 5-S-cysteinyl-dopa increased also in the 3 patients treated on the palms and/or soles (Fig. 4). Here the maximum concentration appeared later, after 11–14 sessions, i.e. 33–40 days after starting treatment. 2 developed no erythema during the course of treatment, and none developed perceptible pigmentation of the palms or soles. In 2 patients (I.S. and B.E.) the psoriasis had cleared completely after 13 and 11 sessions, respectively, and PUVA was discontinued. In the third patient (A.H.) healing occurred after a further month's treatment. The serum concentrations of 5-S-cysteinyl-dopa were not monitored during the last month.

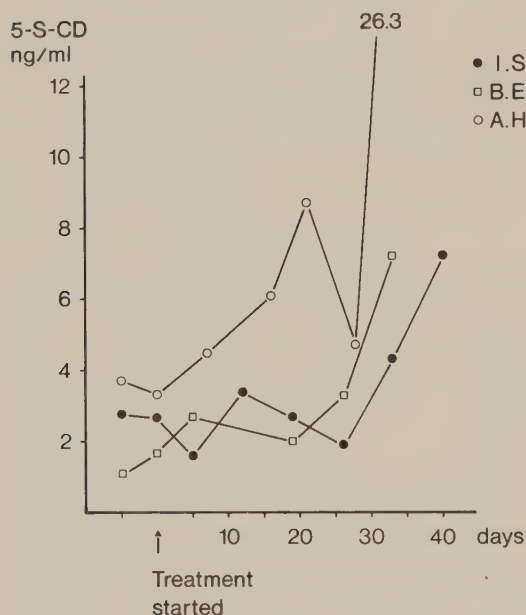


Fig. 4. Serum concentration of 5-S-cysteinyl-dopa in 3 patients treated with PUVA on palms and/or soles.

2. 5-S-Cysteinyl-dopa in serum after exposure to UVA light (VI)

The concentration of 5-S-cysteinyl-dopa in serum just before irradiation was within the normal range (27, 28). After 3 days the 5-S-cysteinyl-dopa values had increased in all persons (Table II and Fig. 5). All now showed increased pigmentation, and all but those with skin type IV had erythematous reactions on the previously non-sunexposed buttock skin. More widespread erythema was observed in 2 skin-type-I individuals. After 4 days the mean concentration in serum was $2 \frac{1}{2}$

times greater than the initial value, and it remained at this level to the end of the experiment (Fig. 5). In 4 persons a further blood sample was collected 18 days after starting irradiation, i.e. 9 days after completing the course of irradiation; in 3 the serum concentrations of 5-S-cysteinyldopa had returned to roughly the initial values, but in 1 (F.N.) the 5-S-cysteinyldopa level remained at about twice the initial value (this man showed one of the greatest increases in serum 5-S-cysteinyldopa at the end of the course of irradiation; Table II). The weakest 5-S-cysteinyldopa response was noted in 2 persons (D.F. and A.M.) with skin types III and IV. Another (B.M.B.), with skin type IV, showed a high 5-S-cysteinyldopa concentration after 10 days. 2 patients with skin types I and II (P.-I.C. and C.B.) showed a marked 5-S-cysteinyldopa response.

Table II. Serum concentrations (ng/ml) of 5-S-cysteinyldopa during UVA irradiation

Individual	Before irradiation		Days after starting irradiation						
			1	3	4	7	8	10	18
P.-I.C.	1.7	1.9	1.9	4.9	6.7	7.7	7.7	8.6	
F.N.	1.8	2.7	4.4	6.3	9.4	5.8	9.0	9.3	5.6
F.N-n.	2.6	2.1	4.1	5.1	5.0	5.4	5.3	4.9	2.2
C.B.	1.8	1.2	2.7	3.2	4.4	5.6	4.8	4.3	
P.O.	1.3	1.3	1.6	2.7	3.2	3.1	3.6	4.4	
U.M.	1.6	2.2	1.6	3.3	4.9	4.7	4.7	5.2	
D.F.		5.0	3.3	5.4	7.4	8.9	6.8	7.4	
B.M.B.	2.4	3.0	5.7	5.6	5.6	4.7	5.5	24.2*	3.9
A.M.	2.5	3.5	4.7	4.1	4.3	3.8	4.8	5.9	3.7
P.S.		2.6	2.8	3.1	7.8	7.5	6.0	5.1	

* Excluded from Fig. 5

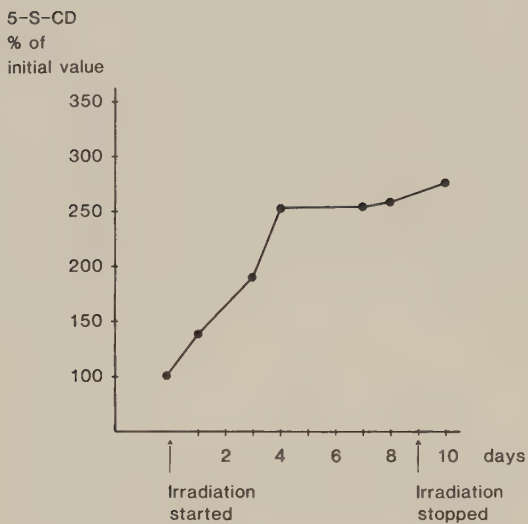


Fig. 5. Mean serum concentrations of 5-S-cysteinyldopa in 10 individuals during UVA irradiation (initial value=100%).

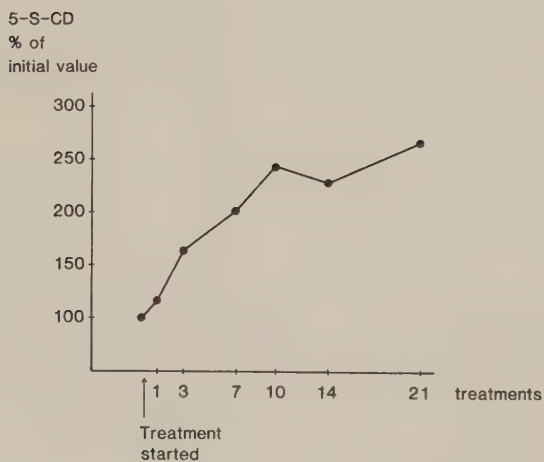


Fig. 6. Mean serum concentrations of 5-S-cysteinyldopa in 12 psoriatics during 5 weeks' UVB treatment (initial value = 100%).

3. 5-S-Cysteinyldopa in serum after treatment with UVB light (VII)

The psoriasis lesions improved in all patients and in 4 they actually cleared after 21 to 28 sessions, i.e. 5-7 weeks' treatment. As the UVB dose was chosen with the aim of eliciting slight erythema, such was noted in all patients after almost every exposure. In none of the patients did treatment have to be stopped because of discomfort. All patients developed tanning, which was most pronounced in 2 with skin type IV.

The serum concentration of 5-S-cysteinyldopa before irradiation was in every case within the normal range (27, 28). After 3 treatments (4 days) 5-S-cysteinyldopa values had increased in all patients (Table III and Fig. 6); by that time erythematous reactions had occurred in all, but no increase in pigmentation could yet be seen. After 10 treatments (17 days) the mean serum concentration was almost 2 1/2 times greater than the starting value, and after 21 treatments (36 days) it was even higher. In 7 patients treatment was continued; the serum values after 28 treatments (49 days) are shown in Table III. In 2 patients the serum 5-S-cysteinyldopa had increased further, but in the other 5 the values were lower than after 21 treatments.

Table III. Serum concentrations (ng/ml) of 5-S-cysteinyldopa during 5 to 7 weeks' of UVB treatment

Patient			No. of treatments						
			1	3	7	10	14	21	28
O.S.		2.4	2.8	4.4	5.3	5.9	6.9	7.2	
P.P.		2.1	1.8	2.2	3.9	6.1	6.8	6.9	
B.J.		1.9	4.0	2.2	3.0	3.5	2.3	5.9	9.4
I.P.		2.7	2.5	6.2	3.1	6.3	7.6	7.7	6.8
A.A.		2.7	3.2	3.9	4.1	4.4	3.2	4.0	
O.H.		5.9	4.5	8.2	7.5	6.1	4.3	7.6	6.3
M.E.		2.7	3.4	3.7	6.6	6.4	5.8	4.8	7.1
Å.B.		2.4	2.7	3.7	6.1	6.7	4.4	3.9	
G.F.		1.5	1.6	4.8	6.6	8.5	6.7	7.3	
I.B.L.	3.0	2.6	2.9	3.1	4.7	5.8	6.0	6.1	3.7
T.J.	3.3	2.1	2.5	3.9	5.1	5.5	5.1	6.2	5.8
G.J.		2.7	3.0	3.7	2.6	5.2	5.8	8.6	5.2

4. Dopa in serum after PUVA treatment (V)

The great majority of the serum dopa values were within the normal range (27, 28), and did not increase during PUVA treatment. In 3 patients (Table IV) high values were occasionally observed before or at the beginning of treatment.

Table IV. Serum concentrations (ng/ml) of free dopa during PUVA treatment

Patient	Before treatment		Days after start of treatment						
			1	3	7	10	14	21	28
K.K.	11	1.9	10	3.0	3.6	2.5	3.5	2.6	
M.G.	4.0	3.0	4.3	8.8	2.3	3.4	2.4	2.6	1.6
A.H.	1.2	1.4	1.8	1.7	2.6	3.4	2.2		
C.N.	2.5	2.1	2.5	2.8	2.5	2.7	2.9		
F.S.	2.5	1.9	2.2	2.2	2.4	2.8	3.3		
A.P.	1.9	1.6	25	7.0	1.8	1.8	3.2	2.2	1.7

C. PIGMENT RESPONSE TO UVA LIGHT IN RELATION TO EXTERNAL PRESSURE (VI)

The immediate pigment darkening (IPD) reaction could be seen when the person turned over on the sunbed after the first 30-min irradiation. It was present over the whole body except for the most prominent parts of the scapulae, the medial sacral areas, the skin over the ventral prominence of the head of the humerus, and the prominent areas of the anterior ribs. These pressure areas showed pallor lasting 1 or 2 seconds after turning or rising from the sunbed, followed by erythema lasting 10–15 min. When the erythema had faded the pressure sites appeared pale in contrast to the general IPD reaction (Table V). The paleness at the pressure sites was seen in 9 of the 10 people, and was most pronounced in lean persons. The only person who did not display areas of weak or absent IPD reaction was a rather obese man. The IPD reaction was most pronounced in individuals with skin skin type IV, and weakest in those with skin type I (Table VI) (7, 59).

Table V. Skin reactions during UVA irradiation in areas exposed to pronounced pressure compared with other skin areas

	Pressure areas	Other areas
Immediate pallor (a few sec. duration)	Yes	No
Immediate erythema (10-15 min. duration)	Yes [*]	No ^{**}
Delayed erythema (starting after 2-3 days)	No	Yes ^{***}
Immediate pigment darkening	No	Yes
Delayed tanning	No	Yes

* This erythema appeared after 30 min. even when the lamps were not switched on, and must therefore have been caused by the pronounced pressure.

** Slight erythema probably caused by the heat sometimes appeared on areas not exposed to pronounced pressure.

*** This erythema was observed on previously non-sunexposed gluteal region.

Table VI. Clinical data on 10 healthy individuals exposed to UVA light

Individual	Age	Sex	Hair colour	Eye colour	Skin type [*]
P-I.C.	32	M	Brown	Blue	I
F.N.	25	M	Brown	Green	I
F.N-n.	29	M	Blond	Green	II
C.B.	25	F	Brown	Brown	II
P.O.	31	M	Brown	Blue	II
U.M.	25	F	Brown	Blue	III
D.F.	25	M	Blond	Blue	III
B.M.B.	24	M	Brown	Brown	IV
A.M.	25	M	Brown	Blue	IV
P.S.	23	F	Blond	Blue	IV

* The following criteria were used: Skin type I = always burn, never tan; II = always burn, then slight tan; III = sometimes burn, always tan; IV = never burn, always tan.

The delayed tanning (DT), which appeared after 2 to 3 days, was most pronounced in people with skin type IV and weakest in those with skin type I. After 2 to 3 days all but the skin-type-IV persons developed an erythematous reaction on the previously non-sunexposed buttock skin (Table V). 2 persons with skin type I (Table VI) developed erythema also on the abdomen and dorsum, and reported itching in these areas lasting for 2 to 3 days. Areas where IPD had been weak or absent also showed weak or absent DT (Fig. 7). No erythematous reaction occurred in these areas, except during the first 10–15 min after irradiation (Table V). Except for the "pressure" erythema these pressure sites therefore remained pale, with no IPD reaction, no "light" erythema, and no DT reaction. After 1 to 2 months these hypopigmented areas were still discernible although the tanning of surrounding skin was fading.

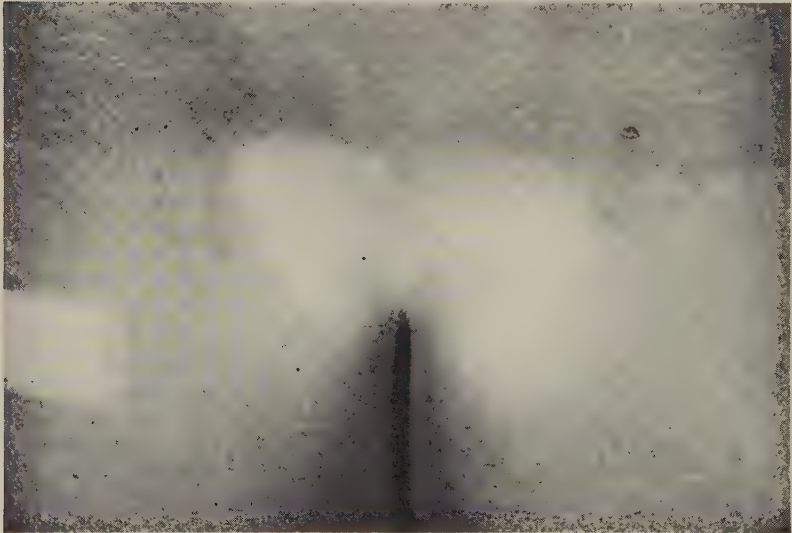


Fig. 7. Lack of pigmentation at pressure sites over the medial sacral area after 10 days' UVA irradiation. Shielded control area on the left.

DISCUSSION

A. EFFECTS AND SIDE EFFECTS OF PUVA TREATMENT OF PSORIASIS

Efficacy of treatment

The efficacy of oral photochemotherapy in clearing psoriasis has been demonstrated in several reports (14, 18, 30, 34, 69, 70, 77, 79, 82, 85, 86, 87, 89). Co-ordinated multicentre studies have been conducted in the United States (50) and Europe (33). In the European study the Department of Dermatology, Lund, participated with its first 117 patients.

Total UVA dose. It is important to keep the total UVA dose low (17, 19, 33, 81). Our therapeutic approach with phototesting of the patients to establish the initial UVA dose combined with cautious UVA dose increments resulted in a low total UVA dose during the initial course of PUVA treatment, which proved to be as effective as more vigorous modes of treatment. In the United States Cooperative Clinical Trial the mean total UVA dose needed for clearing in the initial course was 3 times that in our study (249 J/cm^2 and 80 J/cm^2 respectively). There may be several reasons for this difference. One could be that more patients with skin types IV, V, and even VI were included in the U.S. study, since a greater total UVA dose is required to clear the more sun-tolerant skin types (50). The total UVA dose in our study compared with studies at other PUVA centres is discussed on page 55 in this supplement.

Duration of remission. Psoriasis will generally recur sooner or later after the initial PUVA course. The remission time for patients not given maintenance treatment was on an average 6 months (0.5 to >36 months). Our remission time after PUVA therapy is one of the longest recorded (17, 33, 77, 79, 87).

Maintenance course. As a rule PUVA treatment was stopped after the initial course, and only 34 of 302 patients received maintenance therapy; in these few patients this delayed the recurrence of psoriasis, albeit at the cost of greater UVA exposure. For details of the maintenance course see page 51. Other investigators have shown that remissions induced by PUVA are temporary even with continuous maintenance therapy; once-a-week maintenance treatments did not prevent 50% of patients from relapse within 1 year (50). In the European PUVA study it was shown that within a follow-up period of 80 weeks the chance that a patient will remain in remission is almost the same with or without maintenance therapy (33). However, whereas maintenance treatment failed to prevent a recurrence it did reduce its severity (33).

Repeated courses of PUVA treatment. PUVA was usually discontinued after the initial clearing course, and resumed when relapse occurred. With time more and more patients will undergo repeated courses of PUVA treatment. When comparing the initial course with repeated courses of PUVA it should be remembered that the lesions are often less extensive and severe at the time of retreatment than when the initial course is started.

The repeated courses usually involved 4 sessions per week, like the initial course. However, some patients preferred 2 sessions per week, especially those with long distances to travel and difficulty in getting away from work, but also those who had experienced adverse effects during an earlier course of treatment.

Comparisons between initial (first) and second PUVA treatment courses in 59 of our patients given 4 sessions per week during both courses and not given any maintenance treatment in the intermediate time showed that the number of sessions, the total UVA dose, and the remission time were similar for both courses (Table VI, page 61 in this supplement). In another study with similar total dose for clearing given on fewer occasions the remission time after the second course was considerably briefer (17). In a third study the number of sessions was greater, the time in weeks for clearing was longer and the total UVA dose was higher during a second PUVA treatment course than during the initial course (34).

In 19 patients we compared an initial course of 4 sessions per week with a second course of 2 sessions per week. No maintenance treatment was given in the intermediate period. The number of sessions required for clearing was the same in each, but the course of treatment took about twice as long with 2 sessions per week (Table VII, page 61 in this supplement). The total UVA dose was somewhat higher with 2 sessions per week, because here too the UVA dose was increased once weekly, which means a dose increment at every second session instead of at every fourth. The average remission time was the same after both modes of treatment.

Treatment with 2 instead of 3 or 4 sessions per week during the initial clearing course is commonly used at many centres (44, 50, 70). In the U.S. multicentre study a twice-weekly schedule seemed preferable to three times weekly for skin types I, II, and III because it required less total J/cm^2 and fewer treatments for clearing and less J/cm^2 for maintenance. The better results with the three-times-weekly schedule for skin type IV probably reflect the interference of tanning (50). In the European PUVA study it was emphasized that the total UVA energy requirements for clearing psoriasis

strongly depend on the treatment schedule, and that a schedule of 4 sessions per week might clear the psoriasis before intense pigmentation raises the tolerance of skin to UV radiation (33).

Side effects

Several reports on acute and long-term side effects of PUVA treatment have appeared. Among the acute side effects erythema, pruritus, and nausea seem to be the commonest (33, 50, 70, 81, 85, 89). In the present study the incidence of these three side effects, and especially pronounced erythema, was lower than in most other reports. A possible explanation would be that all our patients were phototested to avoid overdosage of UVA; our cautious dose increments were probably also of importance. A detailed account of other acute side effects that we observed compared with reports from other PUVA studies is given on page 57 in this supplement.

Severe skin pain, a complication previously unreported, was very distressing and occurred in 5% of our patients. It is remarkable that it has not been reported earlier, because it is so dramatic. However, similar cases have been seen recently in Denmark (12), in England (52), in Finland (41), and in Belgium (68). In our patients the pain relapsed if a new treatment course was given with the same treatment schedule as during the initial course, i.e. 4 sessions per week. If however the sessions were reduced from 4 to 2 per week in the same patients, no relapse occurred (84). However, 4 sessions per week are given at many other centres without apparently causing the phenomenon, and the frequency of sessions cannot therefore be the sole explanation of this peculiar side effect, strangely common among our patients. In one patient neurophysiological examination indicated selective stimulation of nociceptive afferents in the skin. PUVA therapy is reported to stimulate the cutaneous nerves and to cause neural invasion into the epidermis (42). Some form of neuritis has been suggested to be the cause of the pain (21).

A form of seborrhoeic dermatitis of the face was a considerably less troublesome complication which is probably fairly common. In the first years of PUVA treatment we did not recognize the facial rash as a specifically PUVA induced phenomenon so the exact incidence cannot therefore be given, but we estimate it to be at least 6%. The symptoms are often mild, appearing after discontinuation of the treatment, and are easily overlooked by the physician; but the patient readily distinguishes these often itching lesions from the ordinary psoriatic lesions. The clinical picture is rather

that of seborrheic dermatitis than of psoriasis. Biopsy was performed in 3 of our patients, and spongiosis without neutrophils was present in all. However, the histological picture of seborrheic dermatitis is not diagnostic (11, 46). During a new PUVA treatment course these facial lesions cleared up before any of the psoriatic lesions; but were also the first to relapse after stopping treatment. If the face was protected during the next course of PUVA no facial rash developed when treatment was discontinued. It is possible that PUVA treatment involves both activation and treatment of latent seborrheic dermatitis. If so, the clinical appearance of the dermatitis would represent a rebound phenomenon due to withdrawal of the PUVA treatment.

There is fear that long-term PUVA treatment might cause degenerative changes of the skin and an increased risk of skin cancer (13, 23). In certain patients increase in nonmelanotic tumours has been recorded (36, 37, 80). Atypical keratinocytes have been found in apparently normal skin (16), and alterations in the melanocyte system have been observed (29, 63, 64, 67, 75, 92, 93).

One of our PUVA-treated patients, a 55-year-old man with skin type I, has developed squamous-cell carcinoma. He has received the highest total UVA dose given at our department (1750 J/cm^2); he has also been exposed to much UVB light over many years, like the only patient in the series who has developed basal-cell carcinoma. The follow-up time is still short, however, and regular examination of PUVA treated patients for skin malignancies is highly important.

"Localized" pigmentary disturbances have occurred in connection with PUVA treatment; any such must be watched for malignant transformation (78). Disseminated small-spotted hyperpigmentation- lentiginosis - is not uncommon after long-term PUVA treatment (8, 41, 54, 78, 83). In our study it occurred in 5 patients who had received an UVA dose of about 1000 J/cm^2 or more. Others maintain that the first pigment manifestations, the total dose of UVA, and the duration of treatment are not correlated (78, 83). Light- and electron-microscopical studies of disseminated hyperpigmentations have shown a great increase in the number of melanocytes in the macules, hyperactivity of the melanocytes, and increased transfer of pigment to dermis and keratinocytes (78); and binucleated cells and signs of melanocytic damage have been reported (78). Similar but less pronounced changes have been seen in the intermacular skin (78). Some of the changes were still apparent 7 months (78) and even 15 months (93) after stopping treatment. As melanocyte changes persist long after PUVA therapy, careful follow-up of these patients is indicated, even though such pigmentary disturbances have hitherto been regarded as harmless (78).

The spotty hyperpigmentation – lentiginosis – observed by us and others differs from the hyper- and hypopigmented changes – mottling – reported from other PUVA studies which developed after severe, UVA-induced erythema and which were associated with atrophic changes, disorganization of epidermal architecture, and cellular irregularities (23, 41).

A third, "localized" pigmentary disturbance reported by others (31, 35) and seen in 2 of our patients was naevus-spilus-like hyperpigmentation, occurring at the site of previous psoriatic lesions.

5 of our patients developed symmetrical spotted hypopigmentations on the upper trunk and arms. These hypopigmentations were not associated with hyperpigmentation (mottling), and had the appearance of pityriasis alba.

Another potential long-term side effect of PUVA treatment is cataract. A case of cataract developing during PUVA treatment has been described, but the correlation with PUVA therapy seems doubtful (66). Follow-up studies on psoralen-treated patients have not disclosed any significant ophthalmological complications (15, 25, 76). Among our patients no such changes attributable to the treatment were seen.

B. LABORATORY STUDIES ON 5-S-CYSTEINYLDOPA AND DOPA

5-S-Cysteinyldopa after exposure to UV light

5-S-cysteinyldopa is a metabolite of all pigment-producing melanocytes, and its oxidation products seem to be components not only of phaeomelanin but of most and perhaps all human melanins (Table VII) (72). 5-S-Cysteinyldopa remains the substance that, better than any other small-molecular melanocytic compound can provide information on the functional state of the melanocyte system (72).

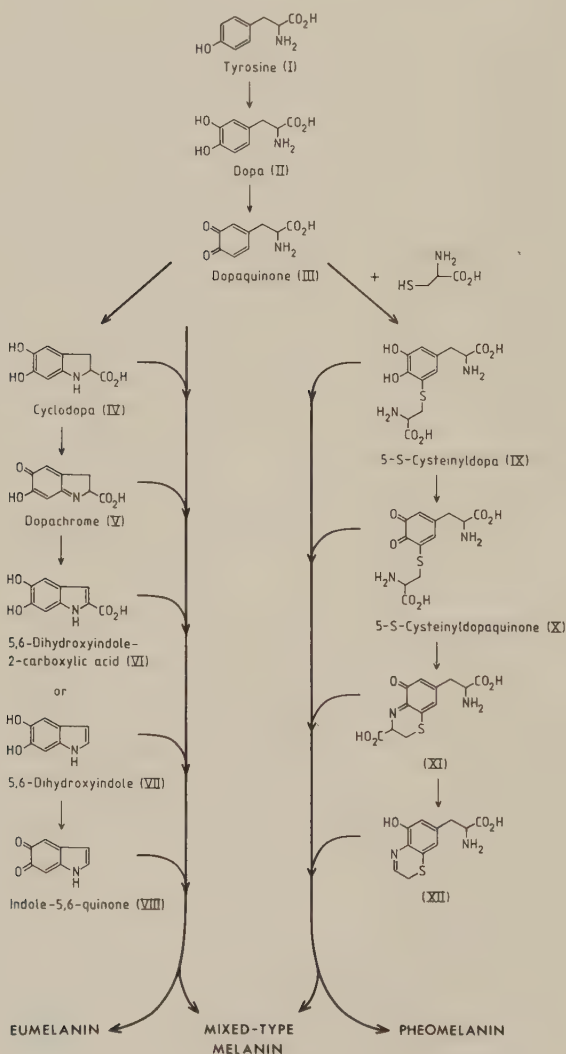


Table VII. The current view of melanin synthesis. (From H. Rorsman et al: Biochemical records of malignant melanoma. In Pigment Cell (ed. R.M. MacKie). Karger, Basel. In press.)

PUVA treatment leads to powerful stimulation of pigmentation. Our studies on 5-S-cysteinyl dopa in urine and serum during PUVA therapy showed a pronounced increase after only 2-3 days of treatment, before any detectable increase in pigmentation had occurred. Peak values were recorded after 1-2 weeks' treatment, when tanning was beginning to become apparent. With continued increase in tanning the 5-S-cysteinyl dopa values first diminished, but a second peak value was noted in 7 of 11 patients followed for 5-7 weeks, and in most cases this was accompanied by pronounced erythematous reactions. Patients showing the smallest increase in serum 5-S-cysteinyl dopa developed only a slight tan and no erythema, and they also showed poor response to treatment.

In the 3 patients given PUVA treatment to palms and/or soles there was a delayed increase in the serum concentrations of 5-S-cysteinyl dopa, which appeared 33-40 days after treatment started. These observations of course require confirmation in a larger series. The observed delayed 5-S-cysteinyl dopa response to PUVA treatment of palms and/or soles could be explained by activation of melanocytes outside the treated skin, as recently described in mice (74). It can be speculated that the observations of elevated human urinary excretion of 5-S-cysteinyl dopa in the spring (71) could also be due to the production of a systematically active melanocyte-stimulating factor, since only a small part of the body is exposed to UV light.

5-S-Cysteinyl dopa concentrations in serum were followed during irradiation with UVA light alone. This is of interest owing to the current profusion of private "clinics" and beauty parlours where UVA is administered for cosmetic reasons. There is also anxiety in medical circles about the marketing of sunbeds for domestic use. All our subjects showed raised serum concentrations of 5-S-cysteinyl dopa after 3 days of irradiation, and some individual concentrations were still higher after 7 to 10 days. After 3 days the delayed tanning (DT) reaction was apparent in all subjects, and at the same time all but those with skin type IV had developed delayed erythema on the previously non-sunexposed gluteal region; people with skin type I had developed more widespread erythema. The inflammatory reactions were not unexpected, because the skin received daily doses of about 20 J/cm^2 of UVA. The minimal erythema dose of UVA is about $20-30 \text{ J/cm}^2$ (62). A great increase in serum 5-S-cysteinyl dopa was noted in the type I individuals who developed marked erythema. The increase in 5-S-cysteinyl dopa was less marked than after PUVA treatment.

On UVB light irradiation all patients showed an increase in serum concentrations of 5-S-cysteinyldopa after 3 sessions; by that time erythematous reactions had occurred in all, but no increase in pigmentation could yet be seen. The mean serum concentration was greatest after 21 sessions, but there were individual variations. All patients developed tanning, but the pigmentation was weaker than with UVA and PUVA. With UVB the erythema response was stronger than with UVA and PUVA. With the defined investigation procedure, i.e. with different treatment schedules for UVB and UVA, the serum concentrations of 5-S-cysteinyldopa increased to almost the same level after exposure to UVB light as after UVA light, but this level was reached later, after about 10 sessions, i.e. 16 days compared to 4 days with UVA light.

The observed increase in 5-S-cysteinyldopa after treatment with different types of UV light could be related to increased activity in the melanocyte and increased numbers of melanocytes. Repeated exposure to PUVA, or UVA, or UVB has been shown to cause marked increase in the number of melanocytes, the number of melanosomes synthesized, the degree of melanization, and the number of melanosomes transferred to keratinocytes (39, 63). Others have found that PUVA treatment leads to a marked increase in melanin production and DOPA activity of the melanocytes but no significant change in the number of DOPA active melanocytes (75).

The increase in 5-S-cysteinyldopa is related to the degree of pigmentation and to inflammatory changes induced by the irradiation, since the highest values for 5-S-cysteinyldopa were accompanied by erythematous reactions. The changes in concentration of 5-S-cysteinyldopa in serum and urine achieved by exposure to different types of UV light reflect important biochemical events in the melanocytes. Further exploration of catecholic amino acid metabolism may prove of great value in the definition of the biochemical effects of increasingly high-intensive UV light systems used for clinical and cosmetic purposes.

Dopa after PUVA treatment

In contrast to 5-S-cysteinyldopa there was no general increase in serum dopa concentrations during PUVA treatment. High dopa values were occasionally observed. We have recently found that methaemoglobin can catalyse the oxidation of tyrosine to dopa and 6-OH-dopa in the presence of ascorbic acid (6). Since small amounts of methaemoglobin are normally present in the blood, this source of error should be watched for in future studies.

In the biochemical diagnosis of melanoma metastases 5-S-cysteinyl-dopa determinations are of much greater value than dopa measurements (4). Current data on 5-S-cysteinyl-dopa and dopa in connection with photochemically induced increase in pigmentation support the view that 5-S-cysteinyl-dopa – and not dopa – is the best marker of the pigment metabolism.

C. PIGMENT RESPONSE TO UVA LIGHT IN RELATION TO EXTERNAL PRESSURE

During irradiation with UVA light on a sunbed the subject lay fairly still on a hard transparent plate of acrylic plastic for 30 min at each session. A few seconds after each irradiation the pressure sites showed reversible erythema – a reactive hyperaemia – indicating transient disturbance of the circulation (24, 53). The erythema disappeared after 10 to 15 min, and failure of pigmentation was then noted at the pressure sites. These patches were observed already after the first UVA irradiation, during the immediate pigment darkening (IPD) phase, which induced contrasting pigmentation on other areas of the body. In 2 people slight immediate erythema on areas not exposed to pronounced pressure was noted during this phase, localized to the abdomen and disappearing after a few hours. Kaidbey and Kligman reported immediate erythema, which persisted for 24 h after exposure to UVA doses of about 50 J/cm^2 . With threshold erythema doses the redness faded after a few minutes. They could not rule out some contribution by heat (40). Others have reported difficulty in differentiating heat erythema from UVA induced immediate erythema (57). Furthermore the erythema is often obscured by the simultaneous appearance of IPD caused by UVA.

Oxygen is needed for the IPD reaction (9, 51, 65), and oxygen deficit at the pressure sites would probably explain the absence of the IPD reaction. However, in 9 of 10 subjects the pressure sites also showed weak or absent delayed tanning (DT), and these areas were still apparent after 1 to 2 months.

The weak or absent DT at pressure sites in our subjects is well known to laymen who use UVA-beds, but seems to have attracted little interest among dermatologists. According to Blum (9), erythema and melanization are not affected by oxygen deprivation during light-exposure. However, oxygen deficiency was probably very pronounced at the pressure sites under our experimental conditions, which may explain our findings concerning erythema and pigmentation. The weak or absent pigmentation of light-exposed skin at pressure sites with low oxygen concentration (24, 53) suggests that light-induced oxygen radicals are of importance for delayed erythema and pigment response to UVA.

SUMMARY

- 302 patients with widespread psoriasis were treated with oral 8-methoxypsoralen photochemotherapy (PUVA) and followed for up to 5 1/2 years after treatment. During the initial treatment course given 4 times a week 96% of the patients showed complete clearing or definite improvement after an average of 26 treatment sessions during 7 weeks and with a total cumulative UVA dose of 80 J/cm². As a rule PUVA was discontinued after the initial course. The average remission time without maintenance treatment was 6 months (range 1/2 to > 36 months). PUVA could be resumed with the same efficacy when the psoriasis recurred.
- The spectrum of side effects was largely the same as registered in other PUVA series, and the commonest were pruritus and nausea. However, 2 previously unreported complications occurred among our patients: 5% developed severe skin pain lasting for up to 3 months, and 6% a form of seborrhoeic dermatitis in the face.
- PUVA treatment leads to powerful stimulation of pigmentation. The chemical events in the melanocytes, as reflected by changes in the concentrations in serum and urine of the melanocytic metabolite 5-S-cysteinyldopa, were analysed during PUVA treatment. Increased concentrations of 5-S-cysteinyldopa were noted after 2-3 days of treatment before any detectable increase in pigmentation had occurred. Peak values were recorded after 1-2 weeks' treatment, when tanning was beginning to appear. The biochemical changes could be related to pigmentation and to inflammatory changes induced by the treatment, since the highest 5-S-cysteinyldopa values were accompanied by erythematous skin reactions.
- The concentrations in serum of 5-S-cysteinyldopa were also recorded after exposure to UV light without psoralen. Exposure to UVA or UVB light led to less pronounced biochemical changes than did the combination psoralen - UVA. The 5-S-cysteinyldopa response was related to pigmentation and to skin inflammation.
- Skin areas exposed to pronounced external pressure (scapulae and sacrum) during UVA irradiation showed no delayed erythema, no immediate pigment darkening (IPD), and no delayed tanning (DT). The weak or absent pigmentation of light-exposed skin at pressure sites with low oxygen concentration suggests that light-induced oxygen radicals are of importance for the development of erythema and for pigment response to UVA.

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Paper I

**ORAL 8-METHOXYPSORALEN
PHOTOCHEMOTHERAPY OF PSORIASIS**

A follow-up study of 302 patients

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Abstract. 302 patients with widespread psoriasis were treated with oral 8-methoxy-psoralen photochemotherapy (PUVA). Complete clearing or definite improvement was obtained in 95.6% of patients. An average of 25.6 treatment sessions with a total cumulative UVA dose of 80.4 J/cm^2 were required for clearing, the duration of the initial PUVA course being 6.9 weeks. Without maintenance treatment patients stayed in remission for on an average 6 months (range 1/2 to >36 months). 50% of the patients received one or more repeated courses of PUVA treatment. The number of sessions, the total UVA dose needed to produce clearing, and the remission time were the same for the first and second courses. One patient developed squamous cell carcinoma. 5% of the patients complained of severe skin pain lasting for up to 3 months. Another side effect not previously described was seborrhoeic dermatitis of the face, observed in 6% of the patients.

Key words: Psoriasis; Photochemotherapy; PUVA; Side effects; Skin pain; Seborrhoeic dermatitis of the face.

Since the introduction in 1974 (27) of systemic photochemotherapy (PUVA) with oral 8-methoxypsoralen (8-MOP) followed by irradiation with high-intensity long-wave ultraviolet light (UVA) for the treatment of severe psoriasis, several reports have confirmed the efficacy of PUVA treatment in clearing psoriasis (7, 8, 13, 32, 33, 34, 36, 41, 47, 50). Co-ordinated multicentre studies have been conducted in the United States (25) and in Europe (15). The Department of Dermatology, Lund, Sweden, participated with its first 117 PUVA-treated patients in the European study (15). The need for keeping the total UVA energy requirements for clearing psoriasis low has been stressed (7, 9, 15, 40). We have had success with rather low total UVA doses, but severe skin pain and seborrhoeic dermatitis of the face, two side effects apparently unusual in other PUVA series, motivate this presentation of 302 patients treated over a period of 5 1/2 years.

MATERIAL AND METHODS

I. PATIENTS

PUVA treatment for severe psoriasis was introduced at this clinic in December 1975. Up to July 1, 1981, 302 patients with psoriasis had been treated, 181 (60%) men and

121 (40%) women (mean age 41.3 years, range 16–78).

Type of psoriasis

All had widespread psoriasis, in most cases (92.7%) of chronic plaque type. 4.3% had guttate psoriasis, 2% pustular psoriasis, and 1% psoriatic erythroderma. The mean duration of illness before the first PUVA treatment was 26.5 years.

Skin types

Before starting treatment the sensitivity to sun and ability to tan were estimated by an established sensitivity scale (25). All were white, and most had skin types II and III (Table I).

Phototesting

To establish the initial UVA dose all patients were phototested in accordance with the principles set out by Wolff et al (51).

II. TREATMENT

20–60 mg of 8-methoxypsoralen (PUVAMET^R, Draco, Lund) according to body weight (0.6 mg/kg) was given, followed by irradiation 2 hours later. The light-source was a high-intensity UVA system (PUVA 4000, Sylvania) with an emission spectrum of 320–390 nm and a peak emission of 365 nm. Patients were instructed to avoid sun exposure on the day of treatment. As a rule no topical medication other than emollients was used, but in some patients with resistant lesions on arms and legs topical steroids were added. Treatment was divided into an initial course, a maintenance course, and repeated courses of PUVA treatment.

Initial course

Patients were treated 4 times weekly until the lesions cleared. As a rule the initial UVA dose was just below the patient's minimum phototoxicity dose (MPD), (established after phototesting), but the highest initial UVA dose was 4 J/cm², even when the MPD was high (5–9 J/cm²). In most patients the UVA dose was increased once weekly, and then by 0.5 J/cm² at each session. "Complete clearing" was defined as the point when more than 95% of the psoriatic lesions had disappeared. Other arbitrarily chosen designations were "definite improvement", "minimal improvement", "no change", and "worse". After the initial course treatment was stopped in most cases.

Maintenance course

After the initial course only about 1/10 of the patients were put on maintenance treatment. In the first year such patients were assigned at random to maintenance treatment, but later this was given only in cases of very severe psoriasis that took comparatively long to clear. The last effective UVA dose in the initial course was used for maintenance treatment, the frequency of sessions ranging from once weekly to once every 2 weeks. If new lesions appeared during maintenance treatment, the UVA dose was increased by 0.5 J/cm^2 at every second session.

Clinical follow-up and repeated courses of PUVA treatment

After the initial course the patients were followed for up to 5 1/2 years. Clinical examination was made every 3 to 6 months with inspection of the whole body. Relapse was defined as the appearance of new lesions or the reappearance of old ones. In most cases a repeated course of PUVA treatment was given when relapse occurred. As a rule the repeated courses involved 4 treatment sessions per week. Some patients, however, received 2 sessions per week, especially those showing adverse side effects during the initial course of treatment, but also patients with long distances to travel and difficulty in getting away from work.

III. CONTROLS

The following laboratory data were recorded before treatment, after 1 and 3 months, and every third month during maintenance treatment: erythrocyte sedimentation rate, haemoglobin concentration, red blood cell count, white blood cell count, thrombocyte count, blood glucose, liver function tests, serum creatinine, urine analysis, and antinuclear antibodies (ANA).

Before treatment ophthalmological examination was performed, with reexamination if a new course of treatment was instituted. During irradiation the eyes were protected with small opaque goggles. All patients were instructed to wear sunglasses conferring protection against UVA throughout the day of medication (49).

Before, during, and after PUVA treatment special attention was paid to naevi and to skin lesions suspected of being malignant, excision and biopsy being done when indicated.

RESULTS

I. SKIN TYPE - PHOTOTESTING

A comparison was made between the patient's skin type and MPD (Table II). In general these were closely correlated, but there was considerable variation in MPD especially in patients with skin types II and III.

II. RESULTS OF TREATMENT

Initial course

Full data on clearing of psoriasis were available for 294 of the 302 patients (see Tables III and IV). "Complete clearing" (231 patients) and "definite improvement" (50 patients) were noted in 95.6% of patients. The average number of exposures required for clearing was 25.6, the duration of the initial course was 6.9 weeks, and the total cumulative UVA dose was 80.4 J/cm^2 . The average UVA dose increment from the first to the last UVA dose during the initial course was 2.3 J/cm^2 (starting with 1.9 J/cm^2 and ending with 4.2 J/cm^2). UVA doses exceeding 10 J/cm^2 were rarely given. The largest UVA dose ever given by us was 11.5 J/cm^2 .

Discontinuation of treatment. During the initial course PUVA was stopped in 13 patients because of treatment failure (Table III - "worse" and "no change or minimal improvement") after 4.7 weeks (range 0.5 - 12 weeks) and 52.5 J/cm^2 (range 2 - 181 J/cm^2). In some of these 13 patients a contributory reason for discontinuation was a side effect, as a rule nausea or pruritus. In general, this group of patients had the most severe psoriasis of the whole series: 5 had chronic plaque psoriasis, 1 guttate psoriasis, 4 pustular psoriasis, and 5 psoriatic erythroderma. In many of them earlier treatment (local remedies, methotrexate, etc.) had failed. In another 6 patients PUVA was discontinued because of side effects, and in 8 for reasons unrelated to treatment (holidays, transport difficulties, etc.). In many of the last-named 14 treatment was broken off at the end of the initial course which had given "definite improvement", and some of them are therefore included in Tables III and IV.

Remission time. 210 of the 231 patients that showed complete clearing during the initial course received no maintenance treatment. 208 were followed up: 182 (87%) had relapsed, whereas 26 (13%) were still in remission. A few patients relapsed after 2 weeks, whereas 1 was still in remission after 36 months. The average remission

time for the 208 patients was ≥ 6.1 months. For the 26 patients still in remission at the time of follow-up the average remission time was ≥ 11.2 months (range $\geq 1.25 - \geq 36$ months).

Maintenance course

34 patients (11.6%) were given maintenance treatment after the initial course. 21 of these patients had shown "complete clearing" and 13 "definite improvement" during the initial course. The maintenance course (treatment once weekly or once every second week) was given over a variable period. In some patients it was discontinued because of side effects or for reasons unrelated to treatment. A few patients with very severe psoriasis received maintenance treatment for up to 5 years, sometimes interrupted by a repeated course of PUVA treatment 2 or 4 times weekly.

Remission time. The 21 patients who showed "complete clearing" during the initial course and who were given maintenance treatment stayed in remission throughout the maintenance course, which lasted for 5 months (average; range 1.5 – 10.5 months). They received on an average 72.6 J/cm^2 (range 24 – 192 J/cm^2) during the maintenance course. After discontinuation of the maintenance course of treatment the patients stayed in remission for ≥ 5.3 months (average; range $\geq 0.5 - 23$ months).

Repeated courses of PUVA treatment

152 patients, i.e. about half of the series, received one or several repeated courses of PUVA treatment after recurrence of the skin lesions (Table V). 126 of them had had no maintenance treatment after the initial course, and 26 had received maintenance treatment. The latter group included a few who were on continuous maintenance treatment.

Comparisons

A. Table VI shows the number of treatments, the UVA dose needed for clearing, and the remission time for the first and second PUVA treatment courses in 59 patients given 4 sessions per week during both courses and not given any maintenance treatment in the intermediate period.

B. Table VII shows a comparison between the number of treatments, duration of treatment courses in weeks, the UVA dose needed, and the remission time for the first and second PUVA treatment courses in 19 patients whose treatment was

changed to 2 sessions per week during the second course of treatment and who received no maintenance treatment in the intermediate period.

Total cumulative UVA dose. Table VIII shows the total cumulative UVA dose in patients given maintenance treatment and/or repeated courses of PUVA treatment.

III. SIDE EFFECTS

After PUVA treatment the patients were followed for up to 5 1/2 years. The interval from starting PUVA to the follow-up investigation is shown in Table IX. 67% of the patients have been followed up for more than 2 years and 17% for over 4 years. Table X shows the acute and long-term side effects observed in 302 patients. The commonest acute side effects were pruritus (16%), nausea (6%), seborrhoeic dermatitis of the face (6%), and skin pain (5%).

Seborrhoeic dermatitis of the face occurred in several patients (45). The exact incidence cannot be given, because during the first 2-3 years of the study seborrhoeic dermatitis was not recognized as a specific feature of PUVA treatment. These patients had practically never previously had any such lesions of the face. After finishing the course of PUVA treatment they complained of itching, red, scaling lesions on seborrhoeic areas of the face. In 3 cases biopsy disclosed seborrhoeic dermatitis but no signs of psoriasis. Untreated, the lesions healed only after several months, but relapsed after a repeated course of PUVA treatment. If the face was protected with a towel during the next course, however, no relapse occurred.

A troublesome side effect of PUVA treatment was extremely severe skin pain. This usually started about 1 week after finishing the PUVA course, came in attacks lasting for several hours, and persisted for 1-3 months. All patients who had pain complained also of itching before, together with, or after the development of pain, and they could readily distinguish between the two sensations. The state was dramatic, and rendered some patients bedridden (43, 44). 5 patients with skin pain were given repeated courses of PUVA treatment when the psoriasis recurred. 3 of the 5 had 4 sessions per week (as during the initial course of treatment), and all developed pain again; 2 were treated only twice weekly during the second course, and had no relapse of pain (44). 1 patient in whom skin pain reappeared during the second 4-day/week course was treated twice weekly during a third course, and this time no pain occurred.

In 12 patients (4%) blisters appeared on apparently normal skin, usually of the feet and legs, and with no preceding erythema. Biopsy showed subepidermal bullae. Direct IF studies failed to demonstrate deposition of immunoglobulins, complement C 3, or fibrinogen.

In 11 patients (3.6%) oedema of the legs occurred, but no other sign of phototoxic reaction such as erythema or blistering.

Viral infection occurred during PUVA treatment in some patients, herpes simplex in 8 and verruca vulgaris in 7.

Infrequent reactions were bleeding under the finger-nails (3 patients), onycholysis (2 patients), and bacterial infections such as erysipelas (1 patient) and folliculitis (2 patients).

Bullous pemphigoid occurred in one patient with very severe psoriasis, which became worse on PUVA treatment. The pemphigoid started 1-2 months after discontinuation of the PUVA treatment at which time the antipsoriatic treatment was topical steroids, only. Biopsy showed a subepidermal bulla with numerous of eosinophils. Direct IF studies showed linear staining of the basement membrane zone with IgG, IgM, IgA, and C 3.

Of the long-term side effects the commonest was "localized" hyperpigmentations, which occurred in 7 patients (2%); this is to be distinguished from the general hyperpigmentation achieved by PUVA treatment. In patients given a total cumulative UVA dose of about 1000 J/cm^2 (Table VIII) disseminated small-spotted hyperpigmentation - lentiginosis - appeared, especially on the flanks, arms, and groins. Biopsy showed in the epidermis slight elongation of the rete ridges and focal basal melanin hyperpigmentation. The melanocytes were slightly distended and rather densely arranged. There were no naevus-cell nests. When PUVA treatment was discontinued the lentiginosis faded slowly. In a few patients the hyperpigmentation was naevus-spilus-like, occurring in earlier psoriatic lesions, and disappeared in time.

Hypopigmentation was seen in 5 patients (1.7%). The lesions were symmetrical, spotty, and localized to the upper part of the trunk and arms. These hypopigmented lesions were seen without the occurrence of hyperpigmentation and had the appearance of pityriasis alba. No fungi could be demonstrated. Biopsy showed uneven basal melanin pigmentation. There was never complete absence of pigment. After discontinuation of treatment these patches of hypopigmentation gradually faded.

Hypertrichosis, usually of the face, was observed in 3 patients (1%). Other long-term side effects were extremely rare. One patient, a 55-year-old man with skin type I, developed squamous-cell carcinomas on the right leg. He was the only patient in the series who received a cumulative UVA dose of more than 1500 J/cm^2 (1750 J/cm^2). He had sunbathed and used artificial UVB light for many years, however. He had never been given arsenic or X-radiation, but for a short time received methotrexate therapy. Another patient, a 60-year-old woman with skin type II, developed a basal-cell carcinoma on the back; she too had been exposed to much solar and UVB radiation over a long period. Another patient developed actinic keratosis on the face.

As a rule laboratory tests were normal. A slight increase in serum transaminases was sometimes noted, in most cases probably due to abuse of alcohol. 2 patients showed a pronounced rise in serum transaminases which returned to normal when PUVA treatment was discontinued. Liver biopsy was not done. Serum antinuclear antibodies (ANA) were studied before and during PUVA treatment: positive tests appeared to be largely transient and unstable, and most became negative.

No ophthalmological changes attributable to the treatment were recorded. No changes in naevi motivating excision were noted.

DISCUSSION

I. EFFICACY OF TREATMENT

The results of this study on 302 patients with widespread psoriasis confirm the favourable response of psoriasis to photochemotherapy observed in other investigations. During the initial course a clearing rate of 95.6% was achieved, requiring 25.6 sessions over a period of 6.9 weeks; the mean total UVA dose needed was 80.4 J/cm^2 . In the United States Cooperative Clinical Trial the clearing rate and number of sessions were similar (25), but treatment took longer because only 2 or 3 sessions per week were given. The total UVA dose needed in the initial course in the U.S. study, on an average 249 J/cm^2 , was 3 times that in our study (25). This may have been because in the U.S. study the UVA doses were determined on the basis of the different skin types, whereas we used phototoxicity testing in all patients, to determine the initial dose. Even though there is fairly close correlation between skin

type and the result of phototesting (Table II), the determination of MPD gives more accurate tuning of the initial UVA dose, because there is great dispersion of MPD within the different skin types. Another reason could be that a schedule of 4 sessions per week might clear the psoriasis before intense pigmentation raises the tolerance of skin to UV radiation. A third explanation might be that our dose increments were cautious, seldom exceeding 0.5 J/cm^2 per week, and that we sometimes found it unnecessary to continue increasing J/cm^2 after the psoriasis started to clear, as has also been found by others (33). However, when comparisons are made it should be emphasized that in the U.S. study more than 12% of the patients had skin type IV, and a small proportion of the patients were not white but had skin-types V and VI. In the U.S. study a greater total UVA dose was required to clear the more sun-tolerant skin types (25); this has also been reported by other investigators (33, 48). Our results tally with the results of the European PUVA study (15), in which our clinic took part with 117 patients. In the European study the total UVA dose was somewhat higher (96 J/cm^2) – possibly because only half of the patients were phototested. However, owing to the different geographical regions participating in the European study there was a wider variation of skin types than in our investigation, more patients belonging to skin-type IV and some even to skin-types V and VI (i.e. sun-tolerant skin types).

After the initial PUVA course the psoriasis will generally relapse sooner or later. The duration of remission is of great importance. Without maintenance treatment our patients stayed in remission for an average of more than 6 months. A few other reports concerning remission after PUVA therapy have been published (7, 15, 34, 36, 47). Our remission time is one of the longest recorded.

Patients receiving maintenance treatment after the initial course were few and to some extent selected. They remained in remission during maintenance treatment and for an average of more than 5 months after stopping treatment. Thus a maintenance course seemed to delay the relapse, albeit at the cost of greater UVA exposure.

With time more and more patients will undergo repeated courses of PUVA treatment. A usual question is whether the results of PUVA treatment are as good after the second as after the initial course. Comparison between initial and second PUVA treatment courses in 59 patients showed that the number of sessions, the total UVA dose, and the remission time were similar in each. In another study (7) the remission time after the second course was considerably briefer; the dosage to clear was similar, but the number of sessions was smaller.

In 19 patients we compared an initial course of 4 sessions per week with a second course of 2 sessions per week. The number of sessions was the same in each, but the course of treatment took more than twice as long with 2 sessions per week. The total UVA dose was also higher, possibly because here too the UVA dose was increased once weekly, which means a dose increment at every second session instead of at every fourth. This dose regimen may not have been necessary, however. The average remission time was the same after both modes of treatment.

When comparing initial and second treatment courses it should be remembered that the extent and severity of psoriasis were as a rule less at the time of retreatment than before the initial course, because all patients had been examined regularly every 3 to 6 months after completing the initial course.

II. SIDE EFFECTS

Several reports on acute and long-term side effects of PUVA treatment have appeared. Among the acute side effects erythema, pruritus, and nausea seem to be commonest (15, 25, 33, 40, 48, 50). In our patients the incidence of these three side effects was lower than in most other reports, especially with regard to pronounced erythema. A possible explanation would be that all our patients were phototested in order to avoid overdosage of UVA; our cautious dose increments were probably also of importance.

Severe skin pain was our most troublesome acute side effect (43, 44), and occurred in 5% of the patients. We find it remarkable that this symptom has not been reported earlier by other investigators, because it is so dramatic and cannot possibly be missed. However, reports of similar cases have recently appeared from other centres (26, 31). Skin pain may be connected in some way with the frequency of sessions (44). However, 4 sessions per week have been given at many other centres without apparently causing this particular side effect. The pathophysiological mechanism remains obscure. PUVA therapy is reported to stimulate the cutaneous nerves and to cause neural invasion into the epidermis (21). Some form of neuritis has been suggested to be the cause (10).

Seborrhoeic dermatitis of the face was another but considerably less troublesome side effect. It appeared a few days or weeks after completing PUVA treatment in patients most of whom had never previously had a facial rash. It is probably fairly common, but because the symptoms are often mild and appear after discontinuation of

treatment the changes may be disregarded by the examining doctor. The fact that seborrhoeic dermatitis could again be provoked by a new treatment course, but only if the face was unprotected during exposure, confirms a causal connection with PUVA treatment (45). This side effect does not seem to have been reported previously. However, it is not clear whether protection of the facial skin has been practised routinely at other centres. The appearance of seborrhoeic dermatitis among our patients further motivates that the face should be protected during PUVA therapy (9).

Phototoxic blisters and localized oedema were not uncommon among our patients, and have also been reported by others (8, 12, 24, 40, 48).

Virus infection during PUVA treatment has been reported (8, 32, 40, 48), despite the fact that DNA function is impaired by PUVA. In our series herpes simplex and verrucae vulgaris occurred.

Bacterial infections such as folliculitis and erysipelas appeared in a few patients, and have also been reported from other centres (8, 32, 48).

Photo-onycholysis (8, 48) and bleeding under fingernails (16) are uncommon side effects of PUVA treatment. We had a few patients with these complications.

Bullous pemphigoid in connection with PUVA therapy has been reported (1, 28, 39, 46). In most patients the bullous lesions started during the PUVA treatment, but one report concerns the development of pemphigoid 4 weeks after cessation of PUVA therapy (2). We had 1 patient who developed pemphigoid 1–2 months after PUVA was discontinued.

Liver damage following 8-methoxypsoralen treatment has been reported (4, 28). We had 2 patients with liver damage.

ANA developing during PUVA therapy has been reported (3, 20), but has not been confirmed by other investigators (11, 23, 37). Some of our patients developed positive tests for ANA during PUVA treatment, but in most cases these became negative.

Disseminated small-spotted hyperpigmentation appears to be the commonest long-term side effect of PUVA treatment, and is usually seen after prolonged therapy (5, 11, 19, 22, 27, 35, 42). In our study it occurred in patients who had received an UVA dose of about 1000 J/cm^2 or more.

Naevus spilus-like hyperpigmentation has also been reported (14, 16); we saw such a reaction in a few patients.

Hypopigmentation with the clinical appearance of pityriasis alba was seen in 5 of our patients after prolonged therapy. These hypopigmented lesions should not be confused with the mottling described in connection with hyperpigmentation (11, 19, 22). The clinical picture was identical in all 5 patients, and this hypopigmentation therefore probably also represents a side effect of PUVA treatment.

Hypertrichosis is another uncommon side effect (8, 16, 40) which occurred in 3 of our patients.

Cutaneous cancer in PUVA-treated patients has been reported during the past few years (6, 17, 18, 22, 38, 40). We saw one patient with squamous-cell carcinoma. He had received the highest total UVA dose given at our department (1750 J/cm^2). He had also received much UVB light over many years, like the only patient who developed basal-cell carcinoma. The follow-up time is still short, however, and examination of PUVA-treated patients at regular intervals seems important.

The present investigation confirms the efficacy of PUVA therapy in severe psoriasis. Our therapeutic approach with phototesting of all patients to establish the initial UVA dose, and comparatively cautious UVA dose increments resulting in a low total UVA dose, has proved to be as effective as other modes of treatment in clearing the lesions. We have found that PUVA can be discontinued after the initial course, and be resumed when relapse occurs. This strategy will probably result in further reduction of the total cumulative UVA energy load, and may improve the long-term safety of PUVA therapy. With low-UVA-dose treatment the incidence of the commonest acute side effects seems to be reduced. The reason why two side effects rarely seen elsewhere – severe skin pain and seborrhoeic dermatitis of the face – occurred among our patients remains obscure.

Table I. Skin types of 302 patients

Skin type	Criteria	% of patients
I	Always burn, never tan	3.6 %
II	Always burn, then slight tan	47.4 %
III	Sometimes burn, always tan	44.4 %
IV	Never burn, always tan	4.6 %

Table II. Correlation between skin type and MPD* in 302 patients

MPD (J/cm ²) Skin type	0.5	1	1.5	2	3	4	5	7	9	No. of patients
I	6	5								11
II	1	24	14	56	35	9	4			143
III			7	6	35	32	34	12	8	134
IV					2	4	4	2	2	14
No. of patients	7	29	21	62	72	45	42	14	10	302

* MPD = the patient's minimum phototoxicity dose

Table III. Results of initial course as determined qualitatively

Qualitative criterion	Number of patients
Worse	5 (1.7%)
No change or minimal improvement	8 (2.7%)
Definite improvement	50 (17.0%)
Complete clearing	231 (78.6%)

Table IV. Summary of results of initial course (294 patients)

Treatment response 'complete clearing' or 'definite improvement'	281 patients (95.6%)
Number of exposures required for clearing (mean)	25.6 treatments
Duration of treatment (weeks) required for clearing (mean)	6.9 weeks
Total cumulative dose required for clearing (mean)	80.4 J/cm ²

Table V. Repeated courses of PUVA treatment

	Number of patients
One new course of PUVA treatment	79
Two new courses of PUVA treatment	35
Three new courses of PUVA treatment	23
Four or more new courses of PUVA treatment	15
Total number of patients who had repeated PUVA treatment	152 (51.7%)

Table VI. Comparison between first (initial) and second PUVA treatment course in 59 patients

	No. of treatments	Total UVA dose (J/cm^2)	Remission time (months)
1st PUVA course	23.6	72.1	5.2
2nd PUVA course	24	75.8	5.8

Table VII. Comparison between 4 sessions per week and 2 sessions per week in 19 patients

	No. of sessions	No. of weeks	Total UVA dose (J/cm^2)	Remission time (months)
4 sessions / week	19.8	4.6	71.7	4.9
2 sessions / week	20.4	10.2	94.9	4.9

Table VIII. Total cumulative UVA dose in patients given maintenance treatment and/or repeated courses of PUVA. (Number of patients 168)

Total UVA dose (J/cm ²)	No. of patients
Less than 100	35
200 - 100	53
400 - 200	45
600 - 400	17
800 - 600	7
1000 - 800	6
1500 - 1000	4
More than 1500	1

Table IX. Interval between initiation of PUVA treatment and follow-up investigation

Interval (years)	< 1/2	1/2-1	1-2	2-3	3-4	4-5	5- 5 1/2
No. of patients (294)	7	32	57	86	62	26	24

Table X. Side effects of PUVA treatment

Side effect	No. of patients	%
<u>Acute side effects</u>		
Pruritus	48	16
Nausea	20	6
Seborrhoeic dermatitis (face)	>20	>6
Skin pain	15	5
Phototoxic blisters	12	4
Localized oedema	11	3.6
Dizziness, headache	8	2.6
Verruca vulgaris	7	2.3
Herpes simplex labialis	4	1.3
Herpes simplex glutealis	4	1.3
Erythema > R ++	3	1
Bleeding under finger-nails	3	1
Erysipelas, folliculitis	3	1
Liver engagement	2	0.7
Photo-onycholysis	2	0.7
Photosensitivity (chlortalidonum)	1	0.3
Bullous pemphigoid	1	0.3
<u>Long-term side effects</u>		
Hyperpigmentation	7	2
Hypopigmentation	5	1.7
Hypertrichosis	3	1
Squamous-cell carcinoma	1	0.3
Basal-cell carcinoma	1	0.3
Actinic keratosis	1	0.3

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APPENDIX

Paper II-VII

Severe Skin Pain after Puva Treatment

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Abstract. Severe skin pain lasting one or two months occurred in 8 of 210 patients treated with PUVA. The pain started 4–8 weeks after the initial dose, mostly about one week after discontinuation of the treatment. It was a prickling, burning pain, usually coming in bouts and confined to limited areas "deep under the skin". In some respects the pain was related to itching, but the patients could easily distinguish between the two sensations. A variety of drugs was tried, but none had any noteworthy effect on this peculiar pain.

Key words: Pain; PUVA treatment

Oral psoralen photochemotherapy (PUVA) can control psoriasis effectively (3, 6, 7) and sometimes ameliorate atopic dermatitis (4), vitiligo (5), and mycosis fungoides (1). During the last 3 years PUVA has been used according to the principles of the European Cooperative Clinical Trial as described by Wolff et al. (7) in the treatment of 210 patients, mostly psoriatics, seen at our department.

The same side effects were observed as those described in other studies on PUVA treatment, viz. erythema, nausea and pruritus (3, 7), as well as less common untoward reactions, such as herpes labialis, hypertrichosis and bleeding beneath the finger nails (2, 4). A further troublesome side effect

Table I. Clinical data about eight patients with pain after PUVA treatment

Patient	Age	Sex	Skin type ^a	MPD (J/cm ²) ^b	No. of treatments	Dose UVA (J/cm ²)	
						Total	Range
1 N. P.	51	M	II	1	26	51.5	0.5-3.5
2 T. J.	54	M	III	3	21	42	2-2.5
3 K. L.	51	M	II	0.5	32	62.5	0.5-3.5
4 S. A.	34	M	III	1.5	24	42.5	1-2.5
5 M. M.	47	F	III	5	15	53	3-4
6 J. F.	25	M	IV	9	17	60	3-4
7 A. P.	35	F	III	3	22	65	2-3.5
8 E. B.	53	F	III	9	15	55.5	3-4.5

^a The following criteria were used: Skintype I = always burn, never tan, II = always burn, then slight tan, III = sometimes burn, always tan, IV = never burn, always tan.

^b MPD = the patient's minimum phototoxicity dose.

of PUVA treatment was severe skin pain, which was noted in 8 of our patients.

CASE REPORTS

Case 1. A 51-year-old man with long-standing psoriasis was treated with PUVA four times a week (Table I). After treatment for 2 weeks, mild transient erythema appeared on the back; after 4 weeks, herpes labialis; and after 6 weeks, intense pain "under the skin" of the trunk. He also reported some itching in the same area. His psoriasis had cleared almost completely and the pain was not confined to previously affected areas. No erythema or other skin lesions were present on the trunk.

The PUVA treatment was discontinued, but the pain persisted. It was most severe at night, even disturbing his sleep. Various analgetics and antihistamines as well as local anaesthetics had no effect on the pain, which persisted for about 2 months, the patient being unable to work for 6 weeks. Itching continued for 1-2 weeks after the pain had stopped (Fig. 1). Laboratory tests revealed nothing remarkable except a transient increase in serum transaminases: S-ASAT 1.9 (normally <0.67 μ kat/l), S-ALAT 2.37 (normally <0.67 μ kat/l). Examination of a biopsy specimen of the liver revealed reactive non-specific hepatocellular changes. No hepatitis Au antigen was demonstrable. Neurologic examination showed nothing abnormal.

Case 2. A 54-year-old man with psoriasis for 30 years was treated with PUVA four times a week for 5 weeks (Table I), after which his psoriasis had cleared and the treatment was discontinued. After treatment for 4 weeks he developed herpes labialis, and after 5 weeks, depigmentation and erythema at the site of a previous discoid psoriatic change over the sacrum.

A few days after the withdrawal of PUVA, severe pruritus occurred in the depigmented area. Two days later the itching changed to severe pain "deep in the skin" in the same area. The pain came in bouts and was most severe at night. An attack could also be provoked by scratching. Each such attack lasted for about 15 min. Various analgetics and antihistamines as well as topical

steroids and local anaesthetics had no noteworthy effect. The bouts of pain persisted for about one month and the patient was unable to work for 2 weeks. Some itching continued for another 2 weeks after the pain had stopped (Fig. 1). Laboratory tests revealed nothing remarkable. The findings at neurologic examination and examination with motor and sensory neurography were normal.

Case 3. A 51-year-old man with psoriasis for 15 years was treated with PUVA four times a week for 8 weeks (Table I), by which time his psoriasis had cleared and treatment was discontinued. During this time the patient had no erythema or any other side effects. One week after discontinuation of treatment the patient got intense pruritus on the back. The itching soon spread to the chest and to the left arm. After about one month the pruritus changed to severe pain in the same areas. No skin lesions were observed. The pain was most pronounced at night and could easily be provoked by scratching. However, it often started spontaneously. Various analgetics and antihistamines as well as transcutaneous nerve stimulation had scarcely any effect. After a further month the pain disappeared from the back, where it had started, and was then confined to the chest and left arm, where it persisted for more than 2 months (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 4. A 34-year-old man with psoriasis for more than 10 years was treated with PUVA four times a week for 6 weeks (Table I), after which about 95% of the affected area had cleared and treatment was discontinued. After treatment for 2 weeks a mild transient erythema had appeared all over the body. One week after discontinuation of treatment the patient complained of a prickling, burning pain "deep under the skin" on the left lower leg and the flanks. He also reported some itching in the same areas. These symptoms were not accompanied by erythema or any other skin lesions. The pain could be provoked by scratching and was most severe at night, when it disturbed his sleep. Various analgetics and antihistamines had no effect. However, transcutaneous nerve stimulation afforded some alleviation from the pain. After one month the pain gradually disappeared over a period of 2 weeks (Fig. 1). Laboratory tests revealed nothing abnormal except an increase in the serum transaminase S-ALAT: 1.3

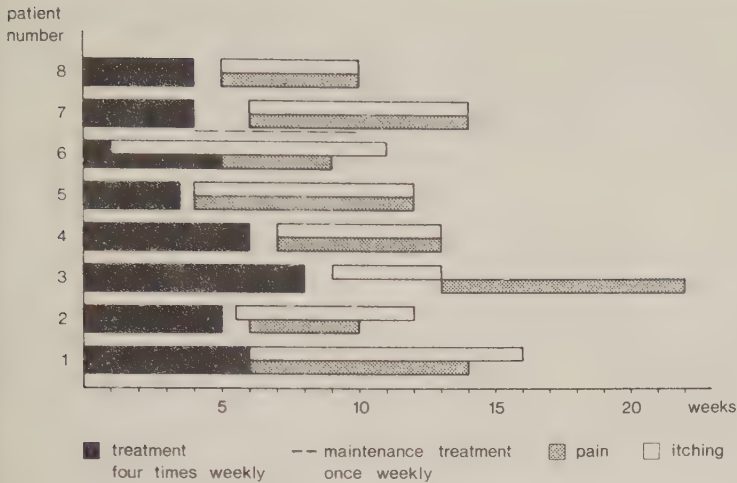


Fig. 1. Duration of PUVA treatment, pain and itching in eight patients.

(normally $<0.67 \mu\text{kat/l}$) which had been observed even before the PUVA treatment.

Case 5. A 47-year-old woman with bronchial asthma and psoriasis since early childhood was treated with PUVA four times a week for 3½ weeks (Table I), after which her psoriasis had practically cleared and the treatment was discontinued. After treatment for 2 weeks she had developed mild erythema on the buttocks and after 3 weeks also on the feet. A couple of days after discontinuation of treatment she complained of itching on the back and abdomen. When the affected area was scratched, the pruritus changed to severe pain "under the skin". At that time she had no erythema or other skin lesions. The symptoms were most severe at night. The itching could be provoked by heat. Pain provoked by scratching generally persisted for about 15 min. Antihistamines and analgetics had no effect. The symptoms persisted for nearly 2 months (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 6. A 25-year-old man with psoriasis for more than 10 years was treated with PUVA four times a week for 5 weeks (Table I). After four treatments he complained of itching on the buttocks. This area was therefore screened off with a piece of cloth during the subsequent treatments. No erythema or any other skin lesions were seen. However, after 5 weeks, the pruritus developed into pain and PUVA was withdrawn. His psoriasis had by then practically cleared. The pain usually started with itching of the skin, which when scratched developed into intense, peculiar, prickling pain "deep in the skin". Usually the attacks lasted for about 20 min, but sometimes for 3 or 4 hours. The symptoms were most pronounced at night and disturbed his sleep. Antihistamines and analgetics had no effect. After about one month the pain subsided, but the pruritus persisted for another 2 weeks (Fig. 1). Laboratory tests revealed nothing remarkable.

Case 7. A 35-year-old woman with severe atopic dermatitis since early childhood was treated with PUVA four times a week for 4 weeks, then once a week for 6 weeks (Table I). The dermatitis had almost cleared, but gradually exacerbated during the maintenance treatment. After two

maintenance treatments she felt a peculiar prickling pain "deep under the skin" on the forearms. After a further 3 weeks the pain spread to the lower legs and the treatment was discontinued. There was mild dermatitis with excoriations not only on the arms and legs, but also on other parts of the body. The prickling pain was most severe at night and could sometimes be provoked by scratching. The pain came in bouts lasting for several hours and sometimes persisted the whole night. Analgetics and antihistamines, topical steroids and local anaesthetics had scarcely any effect. After discontinuation of the PUVA maintenance treatment the pain continued for 3 weeks on the arms and for 4 weeks on the legs (Fig. 1). Laboratory studies revealed nothing remarkable.

Case 8. A 53-year-old woman with psoriasis for more than 30 years was treated with PUVA four times a week for 4 weeks (Table I). The psoriasis had cleared by then and the treatment was discontinued. During treatment the patient experienced no erythema or any other side effects, but one week after discontinuation of treatment she complained of intense itching on the left buttock. The itching could be provoked by exposure to heat and by pressure. Sitting was therefore extremely uncomfortable. When she scratched the skin the pruritus changed to severe pain "deep in the skin". The reaction lasted for about 2 hours. When she scratched the left buttock, she experienced pain also in the dorsal surface of the left lower leg, where she had never noticed any itching. There was neither erythema nor any other skin lesions. The symptoms were most pronounced at night. Antihistamines and analgetics had scarcely any effect. After 4 weeks the pain disappeared from the left leg but persisted on the left buttock for another 1–2 weeks (Fig. 1).

Laboratory studies revealed nothing remarkable. Histopathological examination did not show any abnormal nerve structures. In the upper parts of the corium the capillaries were slightly dilated. Examination by direct immunofluorescence demonstrated fibrinogen in vessels in the whole corium. No demonstrable IgM or C3. The results suggested inflammation at the vessels without complement activation or immunological findings. Neu-

rophysiological examination showed that the appreciation of temperature was intact and equal on both sides. This findings argued against a generalized irritative affection of thin afferent nerve terminals in the skin and indicated a selective stimulation of nociceptive afferents.

DISCUSSION

Of 210 patients treated with PUVA, 8 reported severe pain "deep in the skin". The pain was described in a similar way by all 8 patients. It was of a peculiar type and none of the 8 patients had ever felt anything like it before. At our department such pain has been reported only in these PUVA-treated patients. It was a prickling, burning pain "deep under the skin" and quite different from itching. The pain usually came in bouts lasting 15 minutes up to several hours. The attacks could start spontaneously or be provoked by scratching of or pressure on the skin. They were invariably most intense at night and usually disturbed the patients' sleep. The skin pain occurred in limited areas which did not coincide with the dermatomes.

Itching is a rather common side effect of PUVA treatment. In all these patients the pain had some correlation to itching, which could occur before, after and together with the pain in the same areas (Fig. 1). However, the patients clearly distinguished between these two sensations.

Seven of the patients had psoriasis vulgaris and one had atopic dermatitis. The pain occurred in normal-looking skin unrelated to previous skin lesions except in one patient who had depigmentation and one who had mild dermatitis in the area of the pain.

The pain was related to details in the PUVA treatment in the following respects:

1. It is usually started 1–2 months after the beginning of PUVA treatment (Fig. 1). In 5 of the patients it started about a week after discontinuation of the treatment. In the others the treatment was discontinued because of the pain (Fig. 1).

2. Four patients had mild local erythema during the treatment, but only in case 2 was the pain confined to the area of the preceding erythema. Two of the patients had herpes labialis during the therapy.

3. The total and maximum UVA doses were invariably rather small (Table I). There was no obvious correlation between the occurrence of pain and the skin type and MPD of the patients (Table I).

4. During the treatment the patients used as topical therapy carbamidum 10%, aqua purificata 20%

in a neutral ointment base (ung. Merck®). Furthermore, they used a bath oil containing liquid petrolatum and as emulsifier a synthetic phospholipid (Hostaphat®, Hoechst).

The pain demanded treatment due to its intensity, but various analgetics and antihistamines, topical steroids and local anaesthetics had scarcely any effect. It lasted for 1–2 months and 2 of the patients were unable to work for some weeks. All the 8 patients were emotionally well-balanced persons and reported their symptoms independently of each other. None of the patients could ever think of undergoing this treatment again, even though it had had such a beneficial effect on their skin disease.

In a couple of cases, neurological examination, motor and sensory neurography, histopathological examination and examination by direct immunofluorescence revealed nothing remarkable. In one patient (case 8) neurophysiological examination indicated a selective stimulation of nociceptive afferents in the skin. There were no signs of a generalized peripheral neurotoxic influence. However, the pathophysiological mechanism of this painful side effect of PUVA treatment remains obscure.

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Seborrhoeic Dermatitis of the Face Induced by PUVA Treatment

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Tegner E. Seborrhoeic dermatitis of the face induced by PUVA treatment. Acta Derm Venereol (Stockh) 63: X-X, 1983.

Seborrhoeic dermatitis of the face was observed in 28 of 347 patients treated with PUVA for psoriasis. The facial lesions appeared after discontinuation of PUVA, and had not been present at the start of PUVA treatment. They were prevented by masking the face during irradiation. *Key words: Seborrhoeic dermatitis; PUVA treatment; Rebound phenomenon.* (Received December 3, 1982.)

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During the past 7 years PUVA has been used according to the principles of the European Cooperative Clinical Trial, as described by Wolff et al. (15) in the treatment of 402 patients at the Department of Dermatology, Lund, Sweden. 347 of the patients had psoriasis, and 302 of these are reported elsewhere (13). We have observed the same side effects of PUVA treatment as those reported in other studies, but also 2 apparently uncommon side effects—severe skin pain (11, 12) and seborrhoeic dermatitis of the face. Even though PUVA-induced seborrhoeic dermatitis is common, it seems not to have been reported by others. Four typical case histories are described, each illustrating clinical details found to be significant in this side effect of PUVA treatment.

CASE REPORTS

Case 1.

A 29-year-old woman (skin type III (8); minimum phototoxicity dose (MPD) 9 J/cm² (15)) with a more than 10-year history of psoriasis received three PUVA treatment series during the past 3 years, each series ending in April or May. In the first series, treatment was given four times a week for 4 weeks, with a total UVA dose of 41 J/cm². After five treatment sessions she developed mild erythema on the palms and soles and slight oedema of the feet, which were therefore protected during subsequent irradiations; the UVA dose was temporarily reduced by 1 J/cm². The psoriasis cleared completely, and the patient remained in remission for more than 6 months. One week after PUVA was discontinued, slightly itching, red scaling lesions developed on the forehead and between the eyebrows, with the clinical appearance of seborrhoeic dermatitis. The patient had never previously had a facial rash. She had however had psoriatic lesions on the scalp, and after PUVA treatment she complained of itching of the scalp and of dandruff. No treatment was given, and the facial lesions persisted for about 6 months. A new PUVA treatment series was started 9 months after discontinuation of the first PUVA course, at which time the facial dermatitis had healed. After completing this series, with treatment twice weekly for 6 weeks and a total UVA dose of 44 J/cm², the facial lesions recurred and persisted for a couple of months despite application of a mild steroid. A third relapse of the facial dermatitis occurred after the third series, with sessions four times weekly for 4 weeks and a total UVA dose of 27 J/cm²; this time the rash persisted for more than 5 months.

Case 2.

A 58-year-old man (skin type II, MPD 5 J/cm²) with a 30-year history of psoriasis was given PUVA four times a week for 9 weeks, with a total UVA dose of 105 J/cm². During the treatment series, mild erythema of the face occasionally occurred. After discontinuation of PUVA a facial seborrhoeic rash developed for the first time in the patient's life, located predominantly on the alae nasi and nasolabial folds, but disappearing following treatment with a topical steroid. When the next PUVA treatment series started, the facial skin was normal, but the seborrhoeic dermatitis recurred a few days after

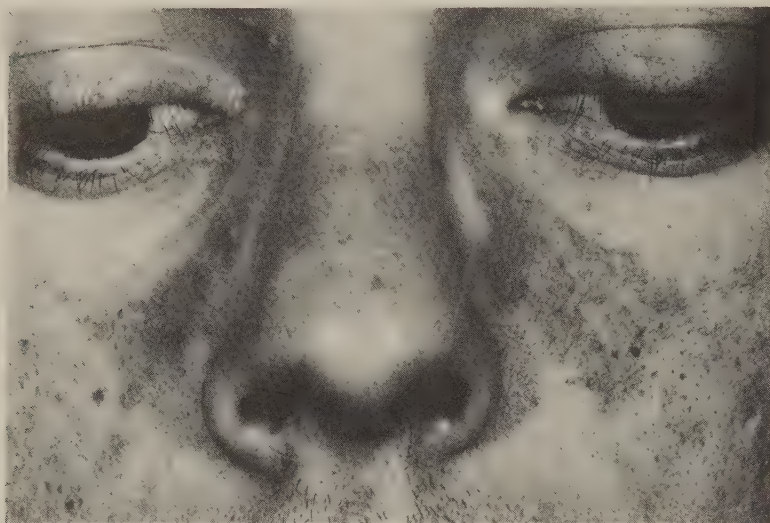


Fig. 1. PUVA-induced seborrheic dermatitis of the face.

ending it. During the following third and fourth treatment series the patient suggested covering his face, and subsequently no facial rash has occurred after stopping PUVA treatment. At every clinical examination, psoriasis of the scalp was present and this did not disappear completely after any of the PUVA courses. Biopsy of forehead skin revealed in the epidermis, areas of focal parakeratosis, dilatation of subepidermal capillaries, and in places lymphocytic invasion of the epithelium with slight spongiosis.

Case 3.

A 55-year-old man (skin type I, MPD 1 J/cm²) with long-standing alcoholism and a 2-month history of widespread, severe psoriasis and psoriatic arthritis was treated with PUVA four times a week for 12 weeks, with a total UVA dose of 98.5 J/cm². The psoriasis cleared completely, and PUVA was discontinued. After a couple of weeks the psoriasis recurred and at the same time seborrheic dermatitis was noted in the nasolabial folds. The patient had never previously had a facial rash. A new PUVA series cleared all the lesions, including those on the face. The patient has since received regular maintenance treatment once a week for nearly $1\frac{1}{2}$ years and subsequently twice monthly.

About 1 month after reducing the treatment to twice monthly, red, scaling, slightly itching lesions developed between the eyebrows and on the cheeks near the nose. No other skin changes were recorded. No erythema occurred on the face or elsewhere during treatment. Biopsy of forehead skin showed in the epidermis spotty parakeratosis and slight spongiosis. There was slight perivascular lymphocytic infiltration in the corium.

Case 4.

A 51-year-old man (skin type III, MPD 3 J/cm²) with a 1-year history of widespread psoriasis involving also the scalp but with no facial lesions was treated with PUVA four times a week for 16 weeks, with a total UVA dose of 143.5 J/cm². After 12 sessions, mild erythema was noted on the chest and abdomen, and these areas were protected during subsequent irradiation. Towards the end of the series the patient felt slight irritation of the facial skin, but no erythema or other lesions were present at this site. He requested protection of his face at the following sessions, and soon after his face had thus been shielded from the UVA radiation, he got red, scaling lesions resembling seborrheic dermatitis on the cheeks near the nose and in the nasolabial folds. This rash subsided temporarily after application of a medium-strength steroid, but after 9 months he still had to apply steroid once or twice a week to keep the lesions under control. At this time he showed no other skin changes and no lesions on the scalp.

Clinical picture

The facial rash had the appearance of seborrheic dermatitis, with red, scaling, often slightly itching lesions located between the eyebrows, in the eyebrows, in the nasolabial folds, and on the cheeks

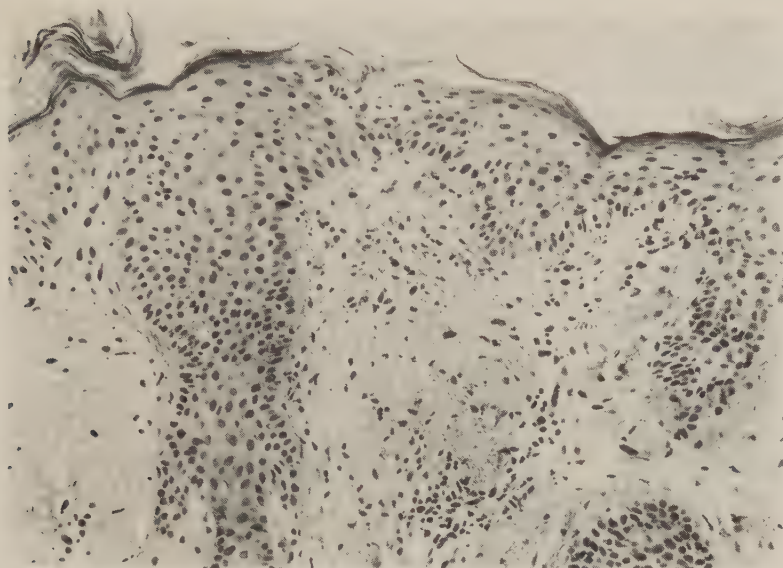


Fig. 2. Spongiosis, patchy parakeratosis and a slight lymphocytic perivascular dermal infiltrate in a patient with PUVA-induced seborrhoeic dermatitis (haematoxylin-eosin, $\times 195$).

near the nose (Fig. 1). Biopsy of skin was performed in 3 patients and the results were in agreement with this diagnosis (Fig. 2). There was often fine scaling of the scalp, sometimes in combination with common psoriasis. One patient also showed lesions on the chest, with the clinical and histological picture of seborrhoeic dermatitis.

Frequency

Among 402 patients treated with PUVA, seborrhoeic dermatitis of the face was observed in 28. The rash occurred only among the 347 patients with psoriasis but not among the 55 with other disorders. The incidence of 8% among the psoriatics is a minimum figure, as during the first 2–3 years of the PUVA follow-up study this complication was not recognized as a side effect of PUVA treatment and was therefore not always recorded.

Relation to PUVA treatment

1. Most patients had never previously noticed any facial rash. A few had previously had very slight, transient lesions, but none showed changes on the face when PUVA was started.

2. The rash always started after the PUVA treatment. The latency time up to its appearance ranged from a few days up to a couple of weeks after discontinuation of the PUVA treatment. In one patient it started when the maintenance course of PUVA treatment was modified from sessions once a week to twice monthly.

3. When patients with induced seborrhoeic dermatitis were given a new PUVA series the facial rash again cleared up but recurred soon after discontinuation of treatment.

4. When in patients who showed facial reactions the face was covered during subsequent PUVA treatment, the rash did not recur. Some of these patients spontaneously requested masking of the face before we became aware of a possible connection between PUVA and the facial dermatitis.

5. Patients with PUVA-induced facial dermatitis appeared to be "sensitive" to the PUVA treatment. Some recalled a burning sensation on the face during irradiation, although no actual rash appeared. In a few others, mild facial erythema occurred during treatment, and in some patients the face was therefore protected with a towel for half of the irradiation time. In this group of patients, localized erythema on other parts of the body was common during treatment; in fact all but 5 of these 28 patients had shown erythematous reactions somewhere on the body during PUVA treatment, often localized to the palms and soles and sometimes associated with oedema of these parts. Five of the 28 patients developed phototoxic blisters on the feet or legs, one showed bleeding under the fingernails, and 4 complained of severe skin pain (11, 12).

6. Of the 28 patients with facial dermatitis after PUVA, one had skin type I and all the others skin types II or III. The MPD varied between 0.5 and 9 J/cm². The total UVA doses given up to the time facial dermatitis was first noted varied between 24 J/cm² and 304 J/cm².

COMMENTS

In all 28 patients the clinical picture was that of seborrhoeic dermatitis. However, the clinical distinction between seborrhoeic dermatitis and psoriasis vulgaris can be difficult. Lesions involving the scalp and face often have features of both states or may change during the period of observation. Terms such as seborrhoeic psoriasis, seborrhoeic-dermatitis-like psoriasis, and psoriasis in seborrhoeico have been used for this condition. The histological picture of seborrhoeic dermatitis is not diagnostic (1, 2, 7). The major difference between psoriasis and seborrhoeic dermatitis is that spongiosis is present in the latter, though only to a slight degree or not at all in psoriasis (7). Biopsy was carried out in 3 of our patients, and spongiosis was present in all samples.

A causal connection with PUVA treatment is likely, owing to 1) the appearance of a facial rash after discontinuation of PUVA in patients who had never previously had dermatitis of the face; 2) the fact that the dermatitis was reinduced by a new treatment series in these patients unless the face was protected during irradiation. It is possible that PUVA treatment means both an activation of and a therapy of a latent seborrhoeic dermatitis. The clinical appearance of the dermatitis would then represent a rebound phenomenon due to withdrawal of the PUVA treatment.

The cause of seborrhoeic dermatitis is unknown. Exacerbation has been described by conditions that increase perspiration (2). Patients undergoing PUVA treatment are usually irradiated in small, enclosed cubicles or cabinets, and this may increase sweating. However, protection of the face with a towel prevented the reaction.

Of the postulated causes of seborrhoeic dermatitis, sebaceous gland dysfunction is the most favoured (2). The sites of predilection of seborrhoeic dermatitis produce the greatest quantities of sebum and have the largest amount of surface fats (4). PUVA treatment has been shown to cause a marked increase in the total lipid (14), and the induced dermatitis may be connected with this.

Although slight erythema is not uncommon during PUVA treatment, it is our impression that patients who developed facial dermatitis also tended to develop erythematous reactions more commonly than did the series as a whole. Patients developing phototoxic blisters and skin pain are also overrepresented in this group (13). Theoretically, the dermatitis could be the result of overtreatment, even though the initial UVA dose was individually determined in all patients after phototesting, for the very purpose of avoiding overdosage of UVA light. The distribution of skin types and the total UVA dose accord with the results in our basic series of 302 patients with psoriasis (13).

The occurrence of seborrhoeic dermatitis of the face after PUVA treatment has apparently not been reported earlier. A few reports have appeared on other conditions classified as 'seborrhoeic diathesis', namely acne-like eruptions, induced by PUVA treatment (6, 9). Seborrhoeic dermatitis of the face induced by PUVA treatment is probably common, but because the rash appears after stopping treatment, it may be disregarded by the doctor. Cutaneous cancer in PUVA-treated patients has been reported (5, 10) and protection of symptomless skin during PUVA therapy has been suggested (3). The facial dermatitis described is yet another reason for masking of the face during PUVA treatment.

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5-S-CYSTEINYLDOPA EXCRETION AFTER TREATMENT WITH 8-METHOXYPSORALEN AND UVA LIGHT

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The excretion of the specific melanocytic metabolite 5-S-cysteinyldopa was studied in patients with psoriasis treated by 8-methoxypsoralen and UVA light. A pronounced increase was found after only 2 days treatment, although no increase in pigmentation could yet be observed. Peak values for urinary 5-S-cysteinyldopa were noted after 1 or 2 weeks treatment. Increase in pigmentation persisted after the excretion maxima for 5-S-cysteinyldopa.

It has recently become possible to trace the metabolism of pigment-producing cells by studying the urinary excretion of the characteristic amino acid of the melanocytes, 5-S-cysteinyldopa. This substance is excreted in the urine by normal subjects, and the quantities vary with sun exposure. In Sweden concentrations are thus low in winter, intermediate in spring and autumn, and high in summer [1]. In patients with melanoma metastases the increased mass of melanin-forming cells is reflected by elevated urinary excretion of 5-S-cysteinyldopa [2,3]. Measurement of the excretion of 5-S-cysteinyldopa is of great value in the investigation of possible metastatic spread in patients with melanoma. However, the moderately increased 5-S-cysteinyldopa excretion due to sun exposure must always be taken into consideration when assessing urinary concentrations in melanoma patients.

It is well known that psoralen-UVA light (PUVA) treatment leads to a strong stimulation of pigmentation. There is an increased number of functionally active melanocytes, and definite morphological changes in the melanocytes have been reported. Melanosomes increase in number, and increased tyrosinase activity of melanocytes has been observed after PUVA treatment [4], but few further data are available on the metabolic changes in melanocytes in this connection. The present study was performed in order to investigate the chemical events in the melanocytes after PUVA treatment as reflected by changes in the excretion of 5-S-cysteinyldopa.

MATERIAL AND METHODS

Patients with psoriasis undergoing treatment with PUVA were chosen for the study [5]. Five Caucasians were investigated, 3 males and 2 females (see the Table). All had severe generalized symmetrical psoriasis but were otherwise healthy. None was receiving drugs. Any exposure to strong sunlight that could have produced erythema antedated the investigation by at least 4 weeks. The investigation took place during the period of February to April 1976.

Oral administration of 8-methoxypsoralen was followed by exposure to a high-intensity long-wave ultraviolet light source emitting

a continuous spectrum between 320 and 390 nm (peak 365 nm) with an energy of 5.6 to 7.5 mW/cm² at 15 cm. Ten-milligram capsules of 8-methoxypsoralen were given two hours before light exposure, according to the patient's weight (30 mg to B.T., L.C., and K.U., and 40 mg to B.L. and U.P.). Initial exposure times were based on the results of phototesting. The patient's minimum phototoxicity dose (MPD) was determined with the aid of 2 × 2 cm template squares and increasing doses of UVA energy (ranging from 0.5 to 9 joules [J]/cm²) 2 hours after ingestion of 8-methoxypsoralen. The erythema was assessed 72 hr after irradiation, and the template square giving barely perceptible, well-defined erythema was taken to correspond to the patient's MPD. The initial dose chosen was well below the MPD in each case. Treatment was carried out 4 times weekly, first on 2 consecutive days, followed by 1 day's rest, with further exposures on 2 consecutive days. The dose was increased once or twice per week, and then by 0.5 J/cm² at each session. The 24-hour specimens of urine were collected immediately before commencing PUVA treatment, after 2 sessions, after treatment for 1 week, and subsequently each week until the lesions had healed. Urine was collected in plastic bottles containing 50 ml of acetic acid and 1 gm of sodium metabisulfite. The 5-S-cysteinyldopa was determined fluorimetrically by a method previously described [6].

Collection of urine was not performed during a time period of 24 hr after intake of 8-methoxypsoralen, since the urine samples then contained a fluorophore that could interfere with our 5-S-cysteinyldopa measurements. After 24 hr there was no further excretion of the fluorescent 8-methoxy metabolite.

RESULTS

Increase in pigmentation was observed in all 5 patients after 1 week's treatment, and pigmentation became more pronounced throughout the period of treatment. The urinary excretion of 5-S-cysteinyldopa before treatment was in every case within the normal range. After only 2 days' treatment it was found to be increased in all patients, but at this time no increase in pigmentation could be seen. Maximum excretion was recorded after 1 or 2 weeks' treatment. At 3 weeks excretion was in all cases lower than at the second week, but the subsequent findings varied from patient to patient. In 4 cases a second increase was observed. In one patient (B.L.) the excretion at 7 weeks was almost as great as the maximum noted after 1 week, and widespread erythema was observed before both excretion peaks. The most striking increases in 5-S-cysteinyldopa excretion were recorded after 1 week in the 2 patients with the lowest MPD values (1.5 and 2 J/cm² respectively), in whom the initial UVA dose was closer to the MPD values than in the other patients; in both these patients erythema preceded the 5-S-cysteinyldopa excretion peak.

The psoriasis lesions cleared up in every patient (in K.U. and U.P. after 5 weeks, B.T. after 6 weeks, B.L. after 8 weeks, and L.C. after 10 weeks). Pigmentation was more prominent in the previously affected skin areas.

DISCUSSION

Marked changes in the 5-S-cysteinyldopa excretion antedated any detectable increase in pigmentation. The raised excretion after 2 days' treatment indicates that stimulation of tyrosinase had already occurred at that time. After 1 to 2 weeks 5-S-cysteinyldopa excretion peaks were recorded, and

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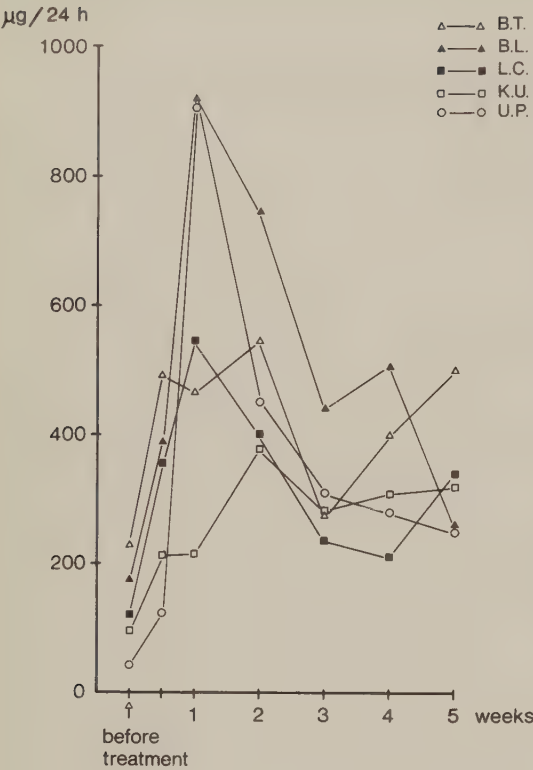
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Abbreviations:

MPD: minimum phototoxicity dose

PUVA: psoralen-UVA light



Urinary excretion of 5-S-cysteinyldopa during PUVA treatment.

tanning was beginning to become apparent. With continued increase in tanning the 5-S-cysteinyldopa excretion first diminished, but another peak value was subsequently noted in 4 of the 5 patients.

The number of functional melanocytes is doubled, and at times tripled, within 3 to 6 days after exposure to 8-methoxypsoralen and long wave ultraviolet radiation [4]. Our findings indicate that the stimulated melanocytes already start excreting more 5-S-cysteinyldopa before pigmentation becomes evident. This might be due to the presence of a less well-developed matrix for pigment deposition at the start of treatment. The consequence of activated tyrosinase leading in turn to increased 5-S-cysteinyldopa formation would then be that the surplus of 5-S-cysteinyldopa formed would be transported out of the cell and excreted.

Clinical and chemical data in the PUVA-treated patients

Patient	Age	Sex	Hair color	Eye color	MPD (J/cm ²)	5-S-cysteinyldopa (µg/24 hr)	
						Initial value	Max. value
1. B.T.	51	♂	Brown	Blue	3	228	545
2. B.L.	29	♂	Brown	Blue	1.5	176	919
3. L.C.	50	♂	Blond	Green	3	120	545
4. K.U.	33	♀	Brown	Blue	7	95	378
5. U.P.	41	♀	Blond	Blue	2	42	906

Another explanation for the lack of correlation between 5-S-cysteinyldopa excretion and pigmentation during the first week might be that 5-S-cysteinyldopa excretion more closely reflects damage to the melanocyte than stimulation of tyrosinase activity. This would be consistent with the observed fall in 5-S-cysteinyldopa excretion after the initial rise in spite of continued and intensified pigmentation. And in fact, erythema reactions preceded the highest 5-S-cysteinyldopa excretion peaks.

In this connection it should be recalled that sun-sensitive individuals with red hair and fair skin show the highest summer excretion of 5-S-cysteinyldopa [1]. It is interesting and provocative that PUVA induces a biochemical change of the same kind as malignant melanoma. However, the excretion of 5-S-cysteinyldopa reflects the metabolic activity of all melanin-forming cells and the increased excretion values observed are probably due to the stimulation of normal melanocytes.

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5-S-CYSTEINYLDOPA AND DOPA IN SERUM DURING TREATMENT WITH 8-METHOXYPSORALEN AND UVA LIGHT

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Abstract. 5-S-Cysteinyldopa and dopa concentrations in serum were studied by high-performance liquid chromatography (HPLC) in patients with psoriasis treated by 8-methoxypsoralen and UVA light. A marked increase in 5-S-Cysteinyldopa was found after 3 days' treatment, although no increase in pigmentation could yet be observed. The highest concentrations of 5-S-Cysteinyldopa in serum were noted after 1 or 2 weeks' treatment. In one patient who showed no increase in serum 5-S-Cysteinyldopa treatment was unsuccessful. During PUVA treatment of 3 patients with psoriasis confined to the palms and/or soles a delayed increase in serum 5-S-Cysteinyldopa was noted after 5 weeks. This delayed response after treatment of a small area of the body is remarkable, and may indicate the formation of a systemic melanocyte stimulation factor. There was no increase in the serum dopa concentrations during PUVA treatment, and dopa analysis was of no value in assessing the activity of the melanocytes. Some unexpectedly high dopa values recorded before and during PUVA treatment may be explained by the fact that dopa originates in the nervous system or the adrenals.

Key words: 5-S-Cysteinyldopa; Dopa; 8-Methoxypsoralen; UVA light; Melanocytes

PUVA treatment leads to strong stimulation of pigmentation. An increased number of functionally active melanocytes has been reported (8, 9, 16), but this finding has not been confirmed by others (12). Melanosomes increase in number (8, 9, 15, 16), and increased tyrosinase activity in melanocytes has been observed after PUVA treatment (9).

Among the metabolites of the melanocytes dopa and 5-S-Cysteinyldopa (5-S-c) have a key role. Both are formed by the action of tyrosinase; dopa from tyrosine, and 5-S-c from dopa by oxidation to dopaquinone followed by nucleophilic addition of cysteine. Urinary excretion of 5-S-c gives a good idea of the serum concentrations of this amino acid, since it is not decarboxylated, but measurement of dopa excretion gives no definite picture of serum dopa concentrations because dopa is to a great extent decarboxylated and also further metabolized (2, 5).

We have previously studied the urinary excretion of 5-S-c in patients with psoriasis treated by 8-methoxypsoralen and UVA light (3). A marked increase took place after only 2 days' treatment, although no increase in pigmentation could yet be observed. Peak values for urinary 5-S-c excretion were noted after 1 or 2 weeks' treatment. Recently a sensitive method for quantitation of 5-S-c and dopa in serum has been described (4).

The aim of the present study was to investigate the chemical events in the melanocytes after PUVA treatment, as reflected by changes in the serum concentrations of 5-S-c and dopa. We also investigated whether PUVA treatment of only the palms and soles altered the serum concentrations of these amino acids.

MATERIAL AND METHODS

13 otherwise healthy psoriatic patients were chosen for the study. All received treatment with PUVA. 10 had widespread psoriasis; 3 had psoriasis of the palms and/or soles. 4 of the 10 patients with widespread psoriasis were studied for 8 days. Blood samples were collected before treatment, and then almost every day for the first 8 days of treatment. The other 6 patients were followed during 28 days' treatment. Blood samples were collected before treatment and after 1, 3, 7, 10, 14, 21, and 28 days' treatment.

The 3 patients with psoriasis of palms and soles (B. E. and A. H.) or soles only (I. S.) were followed during 30-40 days' treatment. Blood samples were collected before treatment and then at intervals of 5-7 days.

No patient was receiving any drug other than 8-methoxypsoralen. There had been no exposure to strong sunlight during the 2-3 months preceding the investigation. The investigation took place during the period October 1979 to March 1980 in order to avoid influence of sun exposure (10). All patients were given 20-60 mg of 8-methoxypsoralen according to body-weight, followed by irradiation after 2 hours; this procedure was carried out four times weekly (13). The light source was a high-intensity UVA system (PUVA 4000, Sylvania) with an emission spectrum between 320 and 390 nm and a peak emission of 365 nm. All 10 patients with widespread psoriasis

Table I. Clinical and biochemical data in patients treated with PUVA

Patient	Age	Sex	Hair colour	Eye colour	Skin type ^a	MPD (J/cm ²) ^b	Initial PUVA dose (J/cm ²)	5-S-Cysteinyldopa (ng/ml)	
								Initial value	Max. value
R. H.	31	♂	Blond	Green	III	1.5	1	2.0	10
F. S.	68	♂	Brown	Brown	II	2	1.5	2.4	12
K. E.	28	♀	Blond	Blue	II	2	2	1.3	7.6
M. G.	50	♀	Blond	Green	II	3	2.5	1.7	12
A. H.	22	♂	Blond	Blue	II	3	2.5	2.7	21
C. N.	40	♂	Blond	Grey	III	3	2.5	4.3	44
A. P.	48	♂	Blond	Blue	II	4	2.5	2.2	6.5
L. C.	53	♂	Brown	Green	IV	3	3	1.3	6.2
C. S.	20	♀	Blond	Blue	III	7	3	2.9	4.1
K. K.	30	♂	Blond	Blue	III	5	3.5	1.3	14

^a The following criteria were used: Skin type I=always burn, never tan; II=always burn, then light tan; III=sometimes burn, always tan; IV=never burn, always tan.

^b MPD=the patient's minimum phototoxicity dose.

were phototested as described by Wolff et al. (14). The initial dose was in most cases well below the minimum phototoxic dose (MPD). The dose was as a rule increased once per week, and then by 0.5 J/cm² at each session.

The 3 patients with psoriasis localized to the palms and/or soles were treated three times a week, local irradiation being provided by a small PUVA unit (PUVA 180 combined with PUVA 200, Sylvania); the initial dose of UVA was 2.5 J/cm², and was increased by 0.5 J/cm² every second time (7).

10 ml venous blood samples for 5-S-c and dopa analysis were collected before and after varying intervals during

PUVA treatment into glass tubes containing 10 mg sodium metabisulphite. Serum was precipitated with 1/10 volume 4 M perchloric acid, centrifuged at 15000 r.p.m., and filtered. 5-S-c and dopa were adsorbed onto Al₂O₃ at pH 8.6, eluted with 0.6 M perchloric acid, and then determined by HPLC and electrochemical detection (4).

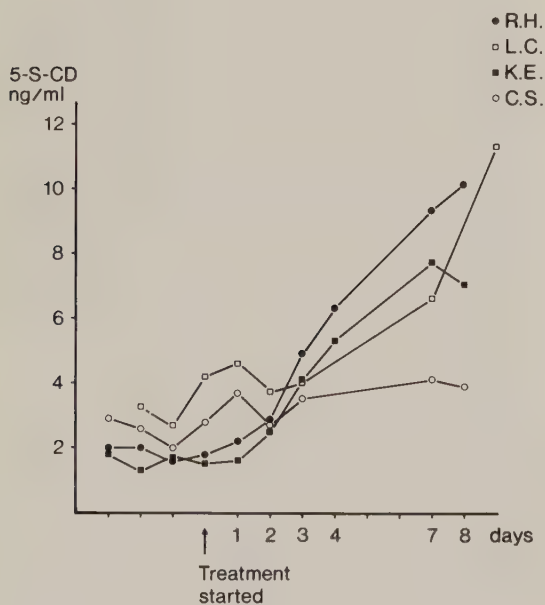


Fig. 1. Serum concentration of 5-S-cysteinyldopa during the first week of treatment.

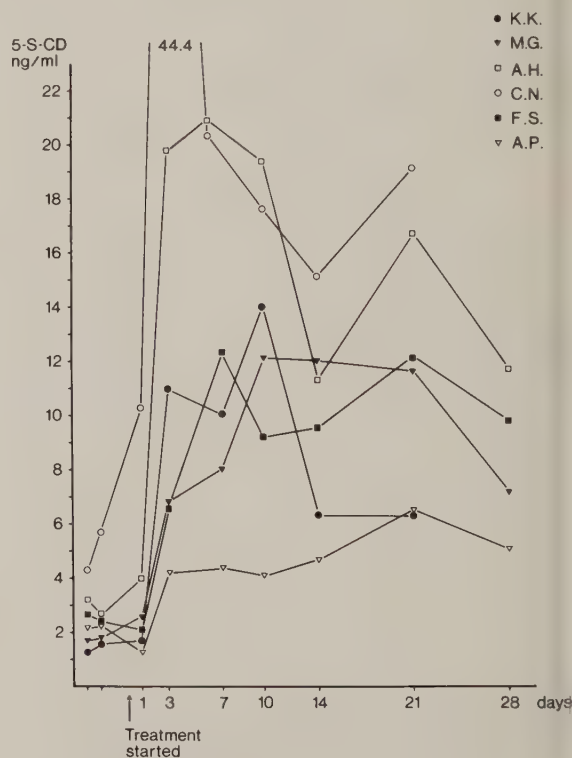


Fig. 2. Serum concentration of 5-S-cysteinyldopa during 4 weeks' treatment.

Table II. Serum concentrations (ng/ml) of free dopa during PUVA treatment

Patient		Before treatment	Days after start of treatment						
			1	3	7	10	14	21	
K. K.	11	1.9	10	3.0	3.6	2.5	3.5	2.6	
M. G.		4.0	3.0	4.3	8.8	2.3	3.4	2.4	1.6
A. H.		1.2	1.4	1.8	1.7	2.6	3.4	2.2	
C. N.		2.5	2.1	2.5	2.8	2.5	2.7	2.9	
F. S.		2.5	1.9	2.2	2.2	2.4	2.8	3.3	
A. P.		1.9	1.6	25	7.0	1.8	1.8	3.2	2.2
									1.7

RESULTS

5-S-Cysteinyl-dopa

Whole-body treatment. The concentration of 5-S-c in serum before treatment was between 1.3 and 4.3 ng/ml (Table 1). These values were within the normal range (5). After 3 days 5-S-c values were increased in all but 2 patients (Figs. 1 and 2). At this time no increase in pigmentation could be seen, but such was first noted after 3–4 treatments. The maximum serum concentration was recorded after 4–6 treatments, i.e. after 7–10 days. In the patients with the highest observed values (Table 1 and Fig. 2) widespread erythema was present at the same time (C. N. and A. H.). The high values observed in some patients after 3 weeks' treatment were accompanied by localized erythema in 2 patients (C. N. and A. H.) or by very marked hyperpigmentation on the knees and medial malleoli in 1 patient (F. S.).

The psoriasis lesions cleared up in 9 of the 10 patients after 3–8 weeks' treatment. 8 of the 9 developed pronounced tanning. Pigmentation was most prominent in the previously affected skin areas. 2 patients (C. S. and A. P.) developed only a slight tan, and the increase in serum concentration of 5-S-c was small (Table 1). In C. S. the psoriasis failed to clear up during PUVA treatment, which was discontinued after 30 sessions. After 18 sessions the serum concentration of 5-S-c was the same as before treatment. As the psoriasis did not respond to treatment the plasma concentration of 8-methoxypsoralen was measured 2 h after taking the drug (6). The 8-MOP plasma concentration was 0.60 $\mu\text{mol/l}$, which is within the normal range. In A. P. the psoriasis cleared up, but recurred only 2 weeks after stopping treatment.

Treatment of palms and soles. The serum concentration of 5-S-c increased also in the 3 patients

treated locally on the palms and/or soles (Fig. 3). Here the maximum concentration appeared later, after 11–14 sessions, i.e. 33–40 days after starting treatment. One (A. H.) showed an increase in serum 5-S-c after seven treatments, when erythema and slight oedema were present on the palms and soles. When the highest serum value was noted (26.3 ng/ml) the erythema and oedema had disappeared completely. The other 2 patients showed no erythema during the course of treatment. None developed perceptible pigmentation of the palms and soles. In 2 patients (I. S. and B. E.) the psoriasis had cleared completely after 13 and 11 sessions, respectively, and PUVA was discontinued. In the third (A. H.) healing occurred after a further month's treatment, but the serum 5-S-c concentration was not monitored during the last month.

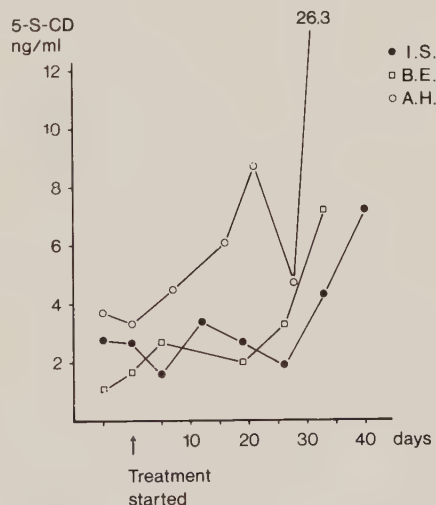


Fig. 3. Serum concentration of 5-S-cysteinyl-dopa in 3 patients irradiated on palms and/or soles.

Dopa

The great majority of the serum dopa values were within the normal range (5) and did not increase during PUVA treatment. In 3 patients (K. K., M. G., and A. P., Table II) high values were occasionally observed before or at the beginning of treatment, without correlation to clinical changes.

DISCUSSION

An increase in serum concentration of 5-S-c was found after only 3 days of treatment, before any detectable increase in pigmentation had been induced. Maximum serum concentrations were recorded after 4–6 sessions. These findings conform to those for urinary 5-S-c during PUVA treatment (3). The 2 patients showing the smallest increase in serum 5-S-c developed only a slight tan. One of them (C. S.) failed to respond to PUVA treatment, although the 8-MOP plasma level was within the normal range. This patient may have been undertreated. As she was fair-haired and blue-eyed an initial PUVA dose of 3 J/cm² was chosen, although the MPD was 7 J/cm². The doses of UVA were designed to give minimal erythema reaction during treatment. In 2 patients who developed pronounced erythema, very high values of 5-S-c were noted at the time of the erythematous reaction. This supports the hypothesis that increased 5-S-c excretion from the melanocytes is rather a reflection of damage to these cells than of pigment production (3). Absence of increase in 5-S-c or of pigment response is probably an indication for more intense treatment.

In the 3 patients given PUVA treatment to palms and/or soles, there was a delayed increase in the serum concentration of 5-S-c which appeared 33–40 days after treatment was started. The absorption and scattering of UVA light may have been so intense in the thick, diseased epidermis that the irradiation could not penetrate to the melanocytes until the stratum corneum had become normal. If this is so, the great increase in 5-S-c after treatment of a small area of the skin is remarkable.

Another explanation must also be considered. If the melanocytes were influenced by the treatment from the start, the number of activated melanocytes may have been too small to produce any detectable increase in serum 5-S-c. Activation of melanocytes outside the treated skin, such as recently described in mice (11), could then explain the delayed in-

crease in 5-S-c. Observations of elevated urinary excretion of 5-S-c in the spring (10) may also conform to the production of a systemically active melanocyte-stimulating factor that need not necessarily lead to increased pigmentation but to morphological and biochemical changes.

There was no increase in the serum dopa concentrations during PUVA treatment. We cannot explain the high dopa values in some of our patients: they could be of extramelanocytic origin, from the adrenals or the nervous system. In the biochemical diagnosis of melanoma metastases, 5-S-c determinations are of much greater value than dopa measurements (1). The present data on 5-S-c and dopa in connection with photochemically induced increase in pigmentation support the view that 5-S-c—and not dopa—is the marker of the pigment metabolism.

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5-S-CYSTEINYLDOPA AND PIGMENT RESPONSE TO UVA LIGHT

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Abstract. 5-S-Cysteinyldopa concentrations in serum were studied in healthy individuals exposed to daily high-intensity UVA radiation. A marked increase in 5-S-cysteinyldopa was found after 3 days, and in some individuals concentrations were still higher after 7 to 10 days. The immediate pigment darkening (IPD) and delayed tanning (DT) were weak or absent at pressure sites, i.e. in skin with a low concentration of oxygen.

Key words: 5-S-Cysteinyldopa; UVA light; Melanocytes; Immediate pigment darkening; Delayed tanning; Pressure sites; Oxygen

Evaluation of the risks and benefits of UVA radiation has achieved considerable importance owing to the proliferation in recent years of private "clinics" and beauty salons for administering UVA for cosmetic reasons. There is also medical concern about the marketing of sunbeds for use at home. The average sunbed consists of a transparent Perspex (polymethyl methacrylate) plate for the subject to lie on, over a bank of UV-emitting fluorescent low-pressure mercury-discharge tubes (4). Skin is exposed, front and back, for about 30 minutes each day. With such a unit the skin might receive 20 J/cm² of UVA, which is roughly twice the dose received during a similar length of time in the tropical midday sun (4).

UVA irradiation causes both immediate and delayed melanin pigmentation (12, 14). We have reported a marked increase in the urinary excretion of the melanocytic metabolite 5-S-cysteinyldopa and increased concentrations in serum of patients with psoriasis after 3 days' PUVA treatment, at which time no pigmentation could be observed. The highest urinary and serum concentrations of 5-S-cysteinyldopa were noted after 1 to 2 weeks' treatment (1, 9).

The aim of the present study was to investigate the chemical events in the melanocytes after exposure to UVA light alone, as reflected by changes in the serum concentrations of 5-S-cysteinyldopa.

MATERIAL AND METHODS

10 healthy volunteers were studied. None were receiving any drugs. There had been no exposure to strong sunlight or other ultraviolet radiation during the 2 to 3 months before the investigation, which took place in December and February in order to avoid influence of sun exposure (15).

The light source was a high-intensity UVA system (Philips TL 85 W/09 T) with an emission spectrum of 310-420 nm and a peak emission of 355 nm. About 0.4% of the radiant energy output of this light source is in the UVB region. The light source consisted of 10 tubes above which was a transparent plate of acrylic plastic for the individual to lie on. Using a Waldmann UVA-meter (H. Waldmann Werk für Lichttechnik, Germany) the intensity of the lamp in the UVA region primarily around the 360 nm band was estimated to 11 mW/cm² just above the plate. Skin was exposed, front and back, for 30 minutes on each side per day on 10 successive days.

10 ml venous blood samples for 5-S-cysteinyldopa analysis were collected in glass tubes containing 10 mg sodium metabisulphite 3 days before and just before the UVA irradiation series was started, and after 1, 3, 4, 7, 8, and 10 days' irradiation. Centrifugation of the samples was at 4500 rpm for 10 min within 1 h. Serum was precipitated with 1/10 volume 4 M perchloric acid, centrifuged at 15000 rpm, and filtered. 5-S-Cysteinyldopa was absorbed onto Al₂O₃ at pH 8.6, eluted with 1 ml 1 M perchloric acid, and then determined by high-performance liquid chromatography (HPLC) and electrochemical detection (6).

RESULTS

Pigment response

The immediate pigment darkening (IPD) and delayed tanning (DT) were studied. A shielded rectangular area on one of the buttocks served as control for judging pigmentation on exposed areas.

The IPD reaction was first seen when the subject turned on the sunbed after the first 30-min irradiation. It was present over the whole body except for the most prominent parts of the scapulae, the medial sacral areas, the skin over the ventral prominence of the head of the humerus, and the prominent areas of the anterior ribs. These areas showed pallor lasting 1 or 2 seconds after turning or rising from the

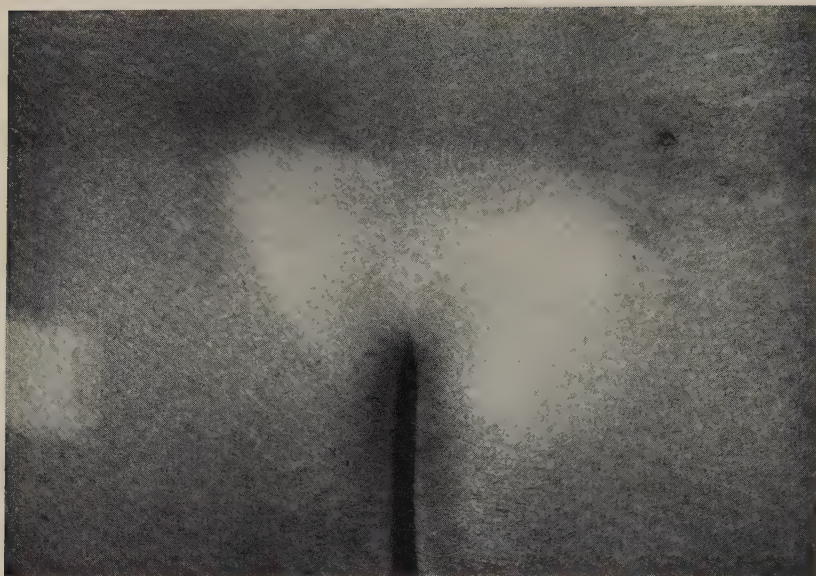


Fig. 1. Lack of pigmentation at pressure sites over the medial sacral area after 10 days' UVA irradiation. Shielded control area on the left.

sunbed, followed by erythema lasting 10–15 min, followed by paling (Table I). The areas of pallor contrasting to the general IPD reaction were seen in 9 of the 10 subjects, and were most pronounced in lean persons. The only subject who did not display areas of weak or absent IPD reaction was a rather obese man. The IPD reaction was most pronounced in individuals with skin type IV, and weakest in those with skin type I (Table II) (2, 12).

The DT, which appeared after 2 to 3 days, was

Table I. Skin reactions during UVA irradiation in areas exposed to pronounced pressure compared with other skin areas.

	Pressure areas	Other areas
Immediate pallor (a few sec. duration)	Yes	No
Immediate erythema (10–15 min duration)	Yes ^a	No ^b
Delayed erythema (starting after 2–3 days)	No	Yes ^c
Immediate pigment darkening	No	Yes
Delayed tanning	No	Yes

^a This erythema appeared after 30 min even when the lamps were not switched on, and must therefore have been caused by the pronounced pressure.

^b Slight erythema probably caused by the heat sometimes appeared on areas not exposed to pronounced pressure.

^c This erythema was observed on previously non-sun-exposed gluteal region.

most pronounced in persons with skin type IV and weakest in those with skin type I. After 2 to 3 days all but the skin type IV subjects developed an erythematous reaction on the previously non-sun-exposed buttock skin. Subjects P-I. C. and F. N. (skin type I) developed erythema also on the abdomen and dorsum, and reported some itching on these areas for 2 to 3 days. Areas where IPD was weak or absent also showed weak or absent DT (Figs. 1 and 2). No erythematous reaction occurred in these areas, except during the first 10–15 min after irradiation (Table I). After 1 to 2 months these hypopigmented areas were still discernible although the tanning of surrounding skin was fading.

Table II. Clinical data on 10 healthy individuals

Individual	Age	Sex	Hair colour	Eye colour	Skin type ^a
P-I. C.	32	♂	Brown	Blue	I
F. N.	25	♂	Brown	Green	I
F. N-n.	29	♂	Blond	Green	II
C. B.	25	♀	Brown	Brown	II
P. O.	31	♂	Brown	Blue	II
U. M.	25	♀	Brown	Blue	III
D. F.	25	♂	Blond	Blue	III
B. M. B.	24	♂	Brown	Brown	IV
A. M.	25	♂	Brown	Blue	IV
P. S.	23	♀	Blond	Blue	IV

^a The following criteria were used: Skin type I = always burn, never tan; II = always burn, then slight tan; III = sometimes burn, always tan; IV = never burn, always tan.

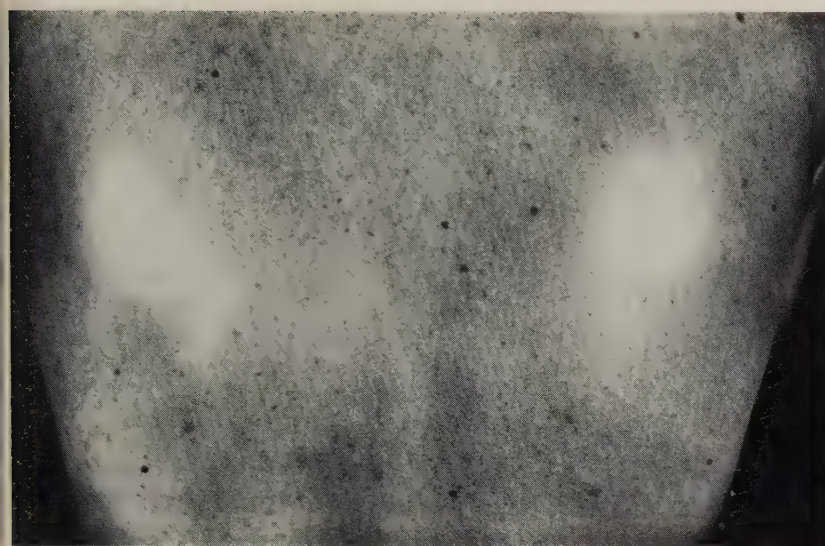


Fig. 2. Lack of UVA-induced pigmentation at pressure sites over the scapulae.

5-S-Cysteinyldopa response

The concentration of 5-S-cysteinyldopa in serum just before irradiation was 1.2–5.0 ng/ml (mean 2.6 ng/ml serum) (Table III), i.e. within the normal range (7, 8). After 3 days 5-S-cysteinyldopa values had increased in all persons (Table III and Fig. 3). All now showed increased pigmentation, and all but those with skin type IV had erythematous reactions. After 4 days the mean concentration in serum was $2\frac{1}{2}$ times higher than the initial value, and it remained at this level to the end of the experiment after 10 days (Fig. 3). In 4 persons a further blood sample was collected 18 days after starting irradiation, i.e. 9 days after completing the course of the irradiation; in 3 the serum concentrations of 5-S-cysteinyldopa had returned to roughly the initial

values, but in 1 (F. N.) the 5-S-cysteinyldopa level remained at about twice the initial value. However, this man showed one of the greatest increases in serum 5-S-cysteinyldopa at the end of the course of irradiation (Table III). The weakest 5-S-cysteinyldopa response was noted in 2 persons (D. F. and A. M.) with skin types III and IV. Another (B. M. B.), with skin type IV, showed a high 5-S-cysteinyldopa concentration after 10 days. 2 with skin types I and II (P-I. C. and C. B.) showed a marked 5-S-cysteinyldopa response.

DISCUSSION

All except persons with skin type IV developed erythema on the previously non-sun-exposed gluteal

Table III. Serum concentrations (ng/ml) of 5-S-cysteinyldopa during UVA irradiation

Individual	Before irradiation		Days after starting irradiation						
			1	3	4	7	8	10	18
P-I. C.	1.7	1.9	1.9	4.9	6.7	7.7	7.7	8.6	
F. N.	1.8	2.7	4.4	6.3	9.4	5.8	9.0	9.3	5.6
F. N-n.	2.6	2.1	4.1	5.1	5.0	5.4	5.3	4.9	2.2
C. B.	1.8	1.2	2.7	3.2	4.4	5.6	4.8	4.3	
P. O.	1.3	1.3	1.6	2.7	3.2	3.1	3.6	4.4	
U. M.	1.6	2.2	1.6	3.3	4.9	4.7	4.7	5.2	
D. F.		5.0	3.3	5.4	7.4	8.9	6.8	7.4	
B. M. B.	2.4	3.0	5.7	5.6	5.6	4.7	5.5	24.2*	3.9
A. M.	2.5	3.5	4.7	4.1	4.3	3.8	4.8	5.9	3.7
P. S.		2.6	2.8	3.1	7.8	7.5	6.0	5.1	

* Excluded from Fig. 3.

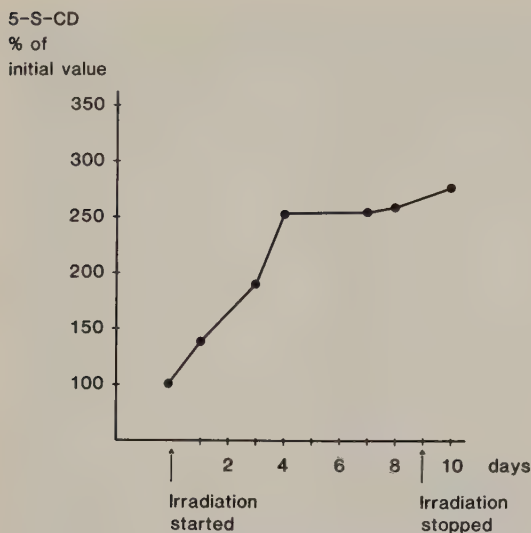


Fig. 3. Mean serum concentrations of 5-S-cysteinyl-dopa in 10 individuals during UVA irradiation (initial value = 100%).

region, and both with skin type I also developed widespread erythema. The erythematous reaction was first observed after 2 to 3 days. The inflammatory reactions were not unexpected, because the skin received daily doses of about 20 J/cm² of UVA. The minimal erythema dose for UVA is about 20–30 J/cm² (13). Detailed data on the time course of the erythematous response to UVA related to the dose of radiation of different wavelengths have been published by Kaidbey & Kligman (10). All our subjects showed increased serum concentrations of 5-S-cysteinyl-dopa after 3 days of irradiation, and some individual concentrations were still higher after 7 to 10 days. PUVA treatment leads to a greater increase in serum 5-S-cysteinyl-dopa (1, 9), and PUVA patients who developed pronounced erythema showed very high 5-S-cysteinyl-dopa concentrations at the time of the erythematous reaction. In the present study a great increase in serum 5-S-cysteinyl-dopa was noted in the type-I individuals who developed marked erythema, a finding which supports the hypothesis that increased 5-S-cysteinyl-dopa excretion from the melanocytes is related more closely to cell damage than to pigment response (1, 9).

The subjects lay fairly still on a hard transparent plate of acrylic plastic for 30 min at each session. After each irradiation the pressure sites showed reversible erythema, indicating transient disturbance of the circulation (5). The erythema disap-

peared after 10 to 15 min, and lack of pigmentation was noted at the pressure sites. These areas of pallor were observed even after the first irradiation, when the IPD reaction was noted on other areas. Oxygen is needed for the IPD reaction (3, 11, 14), and oxygen deficit at the pressure sites would probably explain the absence of the IPD reaction. However, in 9 of our subjects the pressure sites also showed weak or absent DT which could still be observed after 1 to 2 months. The man without obviously weaker pigmentation at pressure sites was rather obese, and had skin type I. His IPD and DT reactions were slight, so any contrasting effect would therefore be weak.

The weak or absent DT at pressure sites observed in our subjects is well known to laymen who use UVA-beds, but seems to have attracted little interest among dermatologists. According to Blum (3), erythema and melanization are not affected by oxygen deprivation during light-exposure. However, the oxygen deficiency is probably very pronounced at pressure sites under our experimental conditions, which may explain our findings of oxygen-dependent erythema and pigmentation. The weak or absent pigmentation of light-exposed skin at pressure sites with low oxygen concentration (5) suggests that light-induced oxygen radicals are of importance for erythema and the delayed pigment response.

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The Effect of UVB Light on Serum Concentrations of 5-S-Cysteinyldopa

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Abstract. 5-S-Cysteinyldopa concentrations in serum were studied in patients with psoriasis treated with UVB light. An increase in 5-S-cysteinyldopa was found after three treatments. The highest values were noted after 5 weeks' treatment.

Key words: 5-S-Cysteinyldopa; UVB light; Melanocytes; Psoriasis

There is a current trend back to the use of UVB phototherapy for psoriasis (2, 3, 9, 10, 11). Comparative studies have been made concerning the efficacy of phototherapy and photochemotherapy (15). Exposure to sunlight leads to increased urinary excretion of the melanocytic metabolite 5-S-cysteinyldopa (13). In a series of investigations we studied the effect of various treatments with artificial light on 5-S-cysteinyldopa (1, 7, 14). We have monitored the urinary excretion and serum concentrations of 5-S-cysteinyldopa in patients with psoriasis treated with PUVA, and found a marked increase in 5-S-cysteinyldopa after 3 days' treatment, at which time no pigmentation had yet appeared. The highest concentrations in urine and serum were noted after 1 to 3 weeks' treatment (1, 7). Recently we have also studied 5-S-cysteinyldopa concentrations in serum in healthy individuals after exposure to UVA light alone, and found a marked increase after 3 days' irradiation and still higher individual concentrations after 7 to 10 days (14). The aim of the present study was to observe the chemical events in the melanocytes after exposure to artificial UVB light as reflected by changes in serum concentrations of 5-S-cysteinyldopa.

MATERIAL AND METHODS

12 otherwise healthy psoriasis patients were included in the study. All were outpatients. The extent of the skin lesions varied between 10% and 50%, i.e. only moderate psoriasis; patients with more generalized disease are given treatment other than UVB light alone. All 12 patients

Table I. *Skin type and pigment data in 12 patients with psoriasis*

The following criteria were used: skin type I = always burn, never tan; II = always burn, then slight tan; III = sometimes burn, always tan; IV = never burn, always tan

Patient	Age	Sex	Hair colour	Eye colour	Skin type
O. S.	39	M	Blond	Blue	II
P. P.	35	M	Brown	Brown	II
B. J.	17	F	Brown	Blue	II
I. P.	71	F	Brown	Blue	III
A. A.	29	M	Blond	Blue	III
O. H.	74	M	Brown	Brown	III
M. E.	31	F	Blond	Blue	III
A. B.	52	M	Brown	Green	III
G. F.	49	F	Blond	Blue	III
I. B. L.	61	F	Brown	Blue	III
T. J.	15	M	Brown	Blue	IV
G. J.	35	F	Brown	Brown	IV

were of the opinion that exposure to sunlight improved their psoriasis. None were receiving any drugs. There had been no exposure to strong sunlight or other UV radiation during the 2 to 3 months preceding the investigation, which was made during November and December to avoid the influence of solar exposure (13).

The light source was a UVB cabin (Waldmann Radiation Unit UV 1000) with an emission spectrum between 280 and 380 nm and a peak emission of 313 nm. The intensity of the lamp in the UVB region was measured with a Waldmann-UV-Meter. The relative spectral sensitivity of the UV-meter has a spectrum of approx. 285–350 nm, with a maximum between 310 and 315 nm. At a distance of 20 cm from the tubes the intensity was estimated to 2.2 mW/cm². The patients received four treatments per week. The initial dose was 20–40 sec, depending on skin type (Table I). As a rule the exposure time was increased by 20–30 sec at each session. The exposure times were chosen to give slight erythema throughout the treatment period.

10-ml venous blood samples for 5-S-cysteinyl-dopa analysis were collected in glass tubes containing 10 mg sodium metabisulphite before the UVB treatment series started, and after 1, 3, 7, 10, 14 and 21 treatments. In 7 patients a further blood sample was collected after 28 treatments. The samples were centrifuged at 4500 rpm for 10 min within 1 h. Serum was precipitated with 1/10 volume 4 M perchloric acid, centrifuged at 15000 rpm, and filtered. 5-S-Cysteinyl-dopa was adsorbed onto Al₂O₃ at pH 8.6, eluted with 1 ml 1 M perchloric acid, and then determined by high-performance liquid chromatography (HPLC) and electrochemical detection (4).

RESULTS

The psoriasis lesions improved in all patients, and in some they even cleared up after 21 to 28 sessions, i.e. 5–7 weeks' treatment. UVB was given

with the aim of eliciting slight erythema or a slight burning sensation after each exposure, and slight erythema was therefore noted in all patients after almost each exposure. If the previous exposure had caused more than slight erythema, the same exposure time was used again. In none of the patients did treatment have to be stopped because of discomfort. All patients developed tanning, which was most pronounced in those of type IV (Table I).

The serum concentration of 5-S-cysteinyl-dopa before irradiation was 1.5–5.9 ng/ml serum (mean 2.6 ng/ml) (Table II), i.e. within the previously defined normal range (5, 6). After three treatments 5-S-cysteinyl-dopa values had increased in all patients (Table II and Fig. 1); by that time erythematous reactions had occurred in all, but no increase in pigmentation could be seen. After 10 treatments the mean serum concentration was almost 2½ times greater than the starting value, and after 21 treatments it was even higher. In 7 patients treatment was continued; the serum values after 28 treatments are shown in Table II. In 2 (B. J. and M. E.) the serum 5-S-cysteinyl-dopa had increased further, but in the other 5 the values were lower than after 21 treatments.

DISCUSSION

All patients showed an increase in serum concentrations of 5-S-cysteinyl-dopa after three treatments.

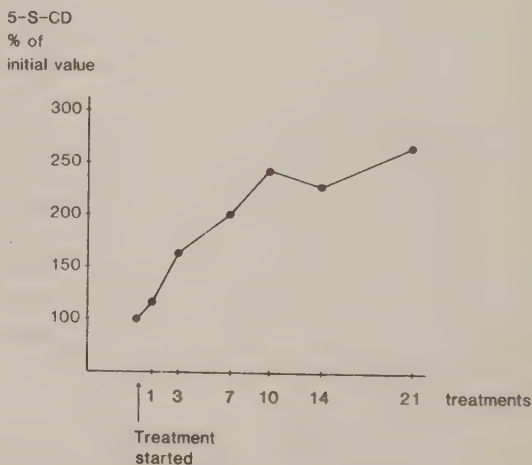


Fig. 1. Mean serum concentrations of 5-S-cysteinyl-dopa in 12 psoriatic patients during 5 weeks' UVB treatment (initial value = 100%).

Table II. Serum concentrations (ng/ml) of 5-S-cysteinyl-dopa during 5 to 7 weeks' treatment

Patient	Before treatment	No. of treatments						
		1	3	7	10	14	21	28
O. S.	2.4	2.8	4.4	5.3	5.9	6.9	7.2	
P. P.	2.1	1.8	2.2	3.9	6.1	6.8	6.9	
B. J.	1.9	4.0	2.2	3.0	3.5	2.3	5.9	9.4
I. P.	2.7	2.5	6.2	3.1	6.3	7.6	7.7	6.8
A. A.	2.7	3.2	3.9	4.1	4.4	3.2	4.0	
O. H.	5.9	4.5	8.2	7.5	6.1	4.3	7.6	6.3
M. E.	2.7	3.4	3.7	6.6	6.4	5.8	4.8	7.1
Å. B.	2.4	2.7	3.7	6.1	6.7	4.4	3.9	
G. F.	1.5	1.6	4.8	6.6	8.5	6.7	7.3	
I. B. L.	3.0	2.6	2.9	3.1	5.8	6.0	6.1	3.7
T. J.	3.3	2.1	2.5	3.9	5.5	5.1	6.2	5.8
G. J.	2.7	3.0	3.7	2.6	5.2	5.8	8.6	5.2

The mean serum concentration was greatest after 21 treatments, but there were individual variations (Table II). PUVA treatment leads to a greater increase in serum 5-S-cysteinyl-dopa, and PUVA patients who developed pronounced erythema showed very high 5-S-cysteinyl-dopa values at the time of the erythematous reaction (1, 7). After exposure to UVA light alone the serum 5-S-cysteinyl-dopa concentrations increased to about the same level as in the present study, but this level was reached earlier, after only 4 days (14). In the UVA study, a great increase in serum value was noticed in the type I individuals, who developed marked erythema. Thus it has previously been observed that the most pronounced increases in 5-S-cysteinyl-dopa occur after UVA or PUVA leading to erythematous reactions. 5-S-Cysteinyl-dopa response is apparently more closely related to cell damage than to the degree of pigmentation resulting from the irradiation.

With UVB the erythema response was stronger, while the pigmentation was weaker than with UVA or PUVA. However, the 5-S-cysteinyl-dopa response was similar to that following UVA irradiation. Our treatment schedules with UVB and UVA were different, and direct comparison of the cysteinyl-dopa responses is not possible. Nevertheless, the present findings are compatible with our earlier hypothesis that elevated 5-S-cysteinyl-dopa levels are more closely related to cell damage than to pigment response (1, 7).

Repeated exposures to UVB is known to cause a marked increase in the number of active melanocytes and in the number of melanosomes (8, 12). The observed increase in 5-S-cysteinyl-dopa may be

related to increased numbers of melanocytes and increased activity in the melanocyte.

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